Chapter 2
Retrosynthetic Analysis of the Compounds with One Functional Group

Abstract A problem-solving approach to retrosynthesis is introduced. Basic principles for good disconnections are postulated. Examples of interconversion and disconnection of carbinols, alkenes, ketones and nitro compounds are discussed. Concepts of *retro*-Diels–Alder and *retro*-Wittig disconnections are presented and the mechanisms of reactions explained. Application of the Wittig reaction on the industrial scale is exemplified by the synthesis of the analog of *bombykol*, the principal of pear odor and anti-appetizer *chlorphentermine*.

2.1 Introduction

A problem-solving approach to retrosynthesis is introduced with examples selected according to the functional group that participates in C–C bond disconnection or is interconverted. The key retrosynthetic steps suggest important synthetic reactions, such as Diels–Alder, cyanhydrin, Wittig and Nef reactions. An argumentation is presented for the feasibility of the Wittig reaction on the industrial scale and its acceptability from the environmental aspect.

The importance of nitroalkanes as building blocks and precursors of *prim*-amines and ketones is exemplified.

Retrosyntheses and syntheses of natural and commercial compounds of medium complexity are presented, such as the analog of the pheromone *Bambykol*, an unsaturated ester principle of pear odor, a key intermediate in the industrial synthesis of β-carotene, and the anti-appetizer *chlorphentermine*.

2.2 Disconnection of Carbinols

In the course of the retrosynthetic analysis of **TM 1**, we met the first example of disconnection with the *participation of one functional group* (Sect. 1.3.1, Scheme 1.10). Participation of the hydroxyl group enabled disconnection of the C–

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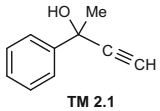
C bond with the formation of two acceptable synthons, a neutral molecule and carbanion with an available reagent or synthetic equivalent.

Now we start with the study of retrosynthesis by the *problem-solving approach*. This approach has characteristics of seminar work promoting knowledge of organic synthesis by retrosynthetic consideration of selected *target molecules*. They are either of commercial or scientific interest, and their retrosynthetic analysis has a certain didactic value. In the next few examples we approach the disconnection of compounds with one functional group, represented by carbinols, and tertiary alcohols.

Example 2.1 Propose good disconnection for **TM 2.1**.



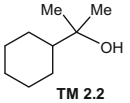
TM 2.1

Which C–C bond is preferably disconnected to the methyl, phenyl or ethynyl group depends on the stability of the carbanion, which appears as the synthon. All disconnections involve *participation of a hydroxyl group*. To evaluate the stability of the resulting carbanions, we consider the acidity of the C–H bond. For methane, pK_a amounts to 42, for benzene 40 and for acetylene 25, revealing the acetylide anion as the most stable (Table 1.2). The corresponding reagent, sodium acetylide, is easily available from acetylene and a strong base, e.g., sodium amide. The preferred disconnection leads to acetophenone **TM 2.1a** and the acetylide anion (Scheme 2.1). Participation of the OH group facilitates the disconnection of the neighboring C–C bond by the formation of the C=O bond in **TM 2.1a** with the departure of a proton.

Disconnection of acetophenone **TM 2.1a** is denoted as *retro*-Friedel–Crafts (*retro*-F.-C.) since its synthesis is completed by the Friedel–Crafts reaction. It is important to note that there is no need to generate the phenyl anion in the synthetic direction since benzene is an acceptable reagent for highly reactive acetyl chloride activated by Lewis acid.

When all groups connected to the carbinol C atom give unstable carbanions, disconnection is guided by an additional principle met in the next example.

Example 2.2 Propose possible disconnections of **TM 2.2** and explain your choice.

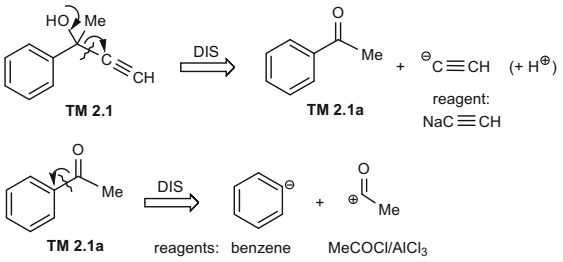


TM 2.2

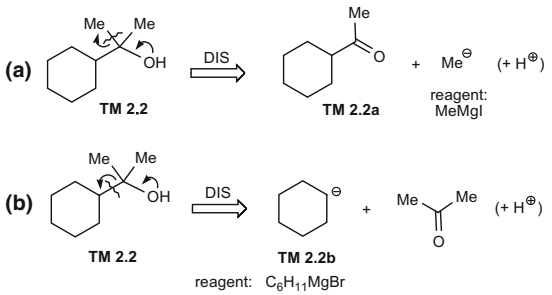
Scheme 2.2 presents disconnections of the methyl and cyclohexyl group. With participation of the carbinolic hydroxyl group, disconnection affords anionic synthons, methyl and cyclohexyl carbanion. Both have proper synthetic equivalents in the corresponding Grignard reagents.

To decide on the preferred disconnection, the second principle of retrosynthetic analysis helps; *preferred disconnection leads to greater simplification of the target*

Scheme 2.1 Preferred disconnection of carbinol **TM 2.1**



Scheme 2.2 Two possibilities for disconnection of **TM 2.2**

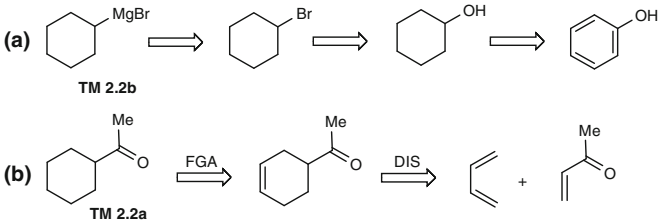


molecule. Maximum simplification of certain target molecules is usually achieved by disconnection, which results in two synthons of *comparable size and complexity*. Size is loosely defined by the number of C atoms in the skeleton and complexity by the number and relative position of functional groups. Greater simplification is obtained for **TM 2.2** by disconnection (b) resulting in two synthons (C_6 and C_3), closer in their dimensions then synthons obtained in disconnection (a) (C_8 and C_1). Besides, by the second disconnection easily available acetone is obtained, different from methyl-cyclohexyl ketone **2.2a**, which requires further retrosynthetic analysis.

This is the moment to consider the availability of the TMs of the second-generation **TM 2.2a** and **TM 2.2b**. Assuming a Grignard reaction in the synthetic direction, cyclohexyl-bromide is needed. On the first glance this immediate precursor of Grignard reagent **TM 2.2b** is more easily available than cyclohexyl methyl ketone **TM 2.2a** (Scheme 2.3). The two-step retrosynthetic analysis of **TM 2.2b** results in phenol, a commodity from the petrochemical industry. Its hydrogenation produces cyclohexanol, which is brominated under standard conditions.

To enter the retrosynthesis of **TM 2.2a**, we need the retrosynthetic tool presented in the following chapters. This is *functional group addition* (Sect. 1.1.2, Table 1.1). Addition of the C=C bond at the proper position in the cyclohexane ring in **TM 2.2a** offers an unexpected opportunity. This FGA leads to a cyclohexene derivative amenable to *retro*-Diels–Alder (*retro*-D.-A.) disconnection to diene and dienophile. The retrosynthetic step and mechanism of the Diels–Alder reaction are discussed in Example 2.4.

According to either of the two retrosynthetic sequences in Scheme 2.3, the synthesis of **TM 2** can be completed from easily available stating materials by



Scheme 2.3 Retrosynthetic analysis of (**a**) **TM 2.2b** and (**b**) **TM 2.2a**

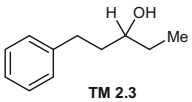
well-known, conceivable reactions. Discussing this example we get acquainted with three basic principles for good disconnection:

- *disconnection should follow* the *correct mechanism*
- *disconnection should follow* the *maximal simplification of* the *target molecule*
- *by the sequence of disconnections we shall arrive at simple, easily available starting materials*

It is important that the principle of maximal simplification of the target molecule cannot be exactly defined or even quantified. Usefulness and easy understanding characterize this principle, like most rules in chemistry.

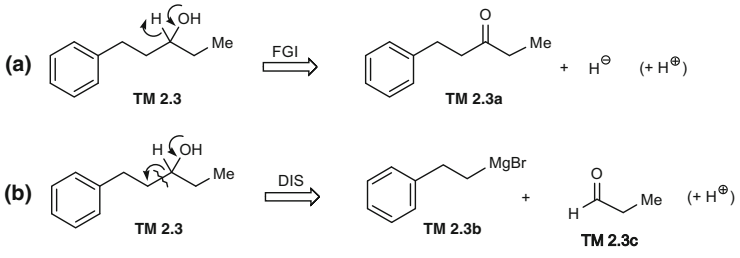
In the former examples we applied a *functional group addition* to create target molecules that are more convenient for disconnection. This concept and other interconversions of functional groups are practiced in the examples that follow.

Example 2.3 Propose retrosynthetic routes from **TM 2.3** either performing *functional group interconversion* or disconnecting the target molecule with participation of the functional group.



Scheme 2.4 presents both retrosynthetic approaches.

FGI (a) with departure of the hydride ion and (easily removable!) proton formally results in a molecule of H_2 beside the carbonyl group. This retrosynthetic step

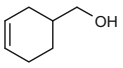


Scheme 2.4 Two retrosynthetic possibilities for **TM 2.3**

formally oxidizes the OH group with elimination of hydrogen. Disconnection (b) results in the formation of carbanion, whose synthetic equivalent is presented in the scheme. As discussed in example 1, disconnection (a) suggests the reduction of ketone **TM 2.3a** in the synthetic step. It is important to note that proposing FGI in Scheme 2.4a, we do not move far along the retrosynthetic road. Formally, any FGI with heterolytic disconnection of the C–X bond might be considered an internal redox process; the C atom is oxidized to carbocation and the heteroatom or hydrogen atom reduced to an anion. Interconversion of the functional group to a higher or lower oxidation state makes sense only when it leads to more easily available TM of the next generation. This is not the case with **TM 2.3a**, however.

The second retrosynthetic route (b) comprises disconnection of the C–C bond triggered by participation of the neighboring OH group. Grignard reagent **TM 2.3b** is presented for the carbanionic synthon, and the second one is the neutral molecule propanal **TM 2.3c**; both are available starting materials.

Example 2.4 Propose the retrosynthesis then synthesis of **TM 2.4**.

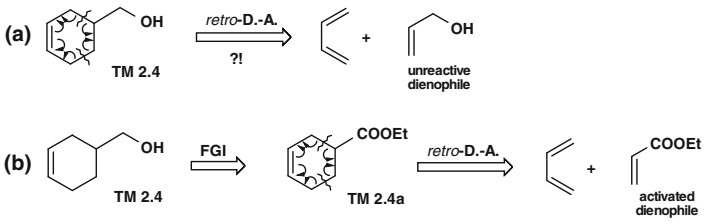


TM 2.4

This example requires more retrosynthetic imagination. We recognize the cyclohexene ring with the hydroxymethyl group in the β position of the C=C bond and consider a possible precursor for the cyclohexene ring. The benzene derivative can be excluded for good reason since partial and regioselective reduction to the substituted cyclohexene derivative represents a formidable task.

The second possibility conceives the construction of a cyclohexene ring from the proper building blocks and suggests *retro*-Diels–Alder disconnection of the cyclohexene derivative. Here we apply disconnection of two bonds resulting in two synthons, as explained in Sect. 1.1.1, Scheme 1.2, and presented for **TM 2.4** in Scheme 2.5.

The *retro*-Diels–Alder step envisages *homolytic disconnection* of two bonds in the 2,3-position related to the double bond of the cyclohexene ring. Two electrons of each σ bond and two electrons from the π bond move to the neighbor σ bonds (Scheme 2.5a). Such disconnection corresponds to the *pericyclic* or *concerted* character of the Diels–Alder reaction [1, 2].



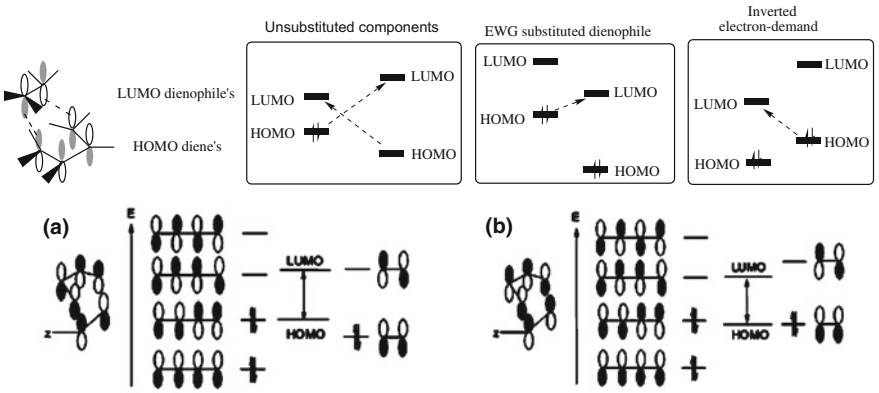
Scheme 2.5 The *retro*-Diels–Alder disconnection of **TM 2.4**

Note The concerted mechanism in the Diels–Alder reaction implies the 4π-2σ cycloaddition of two reacting partners, diene and dienophile [3–7]. To affect the productive interaction, the formation of two σ bonds, they should possess the proper electronic properties of their frontier orbitals HOMO and LUMO. The energy barrier for this reaction is lowered by the closer energies of diene's HOMO and dienophile's LUMO. This is achieved by electron-donating groups (EDG) in diene and electron-withdrawing groups (EWG) in dienophile (Scheme 2.6).

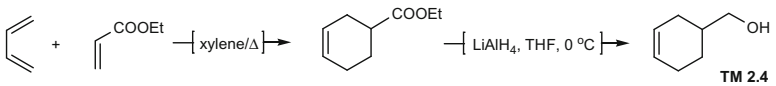
retro-Diels-Alder disconnection obeys the first rule of retrosynthesis by following the correct mechanism. Exactly for mechanistic reasons, however, the synthesis of **TM 2.4** from butadiene and allyl alcohol will fail! Disconnection (a) in Scheme 2.5 results in the unfavorable couple diene-dienophile since ethylene is substituted with the hydroxymethyl group, a weak electron-donating group rising from LUMO energy. This energetic mismatch is solved by route (b) where we first perform FGI of the hydroxymethyl group to a strong electron-withdrawing carbethoxy group in **TM 2.4a**. This retrosynthetic step leads to the reactive couple diene-dienophile.

The example of **TM 2.4** also serves to illustrate the importance of the order of retrosynthetic steps to propose a workable synthetic route (Scheme 2.7).

The last example in this section applies the former retrosynthetic concepts in a new way.

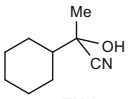


Scheme 2.6 HOMO-LUMO orbitals in butadiene and ethylene and interaction of diene and dienophile



Scheme 2.7 Proposal for the synthesis of **TM 2.4**

Example 2.5 Suggest retrosynthesis then propose the synthesis of **TM 2.5**.



TM 2.5

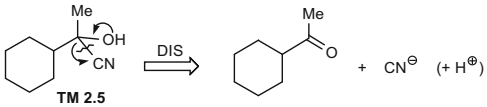
Disconnection of any C–C bond from the carbinol C atom can be completed with participation of the hydroxyl group, avoiding the formation of an unstable cationic synthon. The stable cyanide anion is the preferred carbanionic synthon in the disconnection of **TM 2.5** (Scheme 2.8).

Note There are many useful reagents for the cyanide ion, from inorganic salts (NaCN, KCN) to organic cyanides (R_3SiCN, NH_4CN). **TM 2.5** contains geminal hydroxyl and cyano groups. The proposed disconnection represents the *retro*-cyanohydrin step. The *cyanohydrin reaction* is the standard route to α-hydroxy acids available on hydrolysis of cyano groups [8]. The chiral variant of this reaction is particularly important for the synthesis of biologically active compounds in an enantiomerically pure form [9, 10].

Synthon **TM 2.5a** is a neutral molecule, cyclohexyl methyl ketone. To the synthetic chemist acetophenone might spring to mind as an obvious next-generation target because of the structural relation to **TM 2.5a**. Exhaustive hydrogenation of this aromatic ketone is expected to give 1-cyclohexylethanol **TM 2.5b**, which can be oxidized to ketone by various protocols, e.g., by pyridinium chlorochromate (PCC, Scheme 2.9).

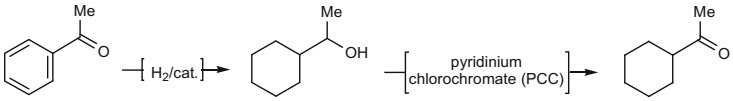
This is not a workable route, however, since the hydrogenation of acetophenone is not chemoselective and results in a mixture of products, 1-phenylethanol, ethyl benzene and ethyl cyclohexane, besides 1-cyclohexylethanol [11, 12]. The highest reported selectivity for **TM 2.5b** was 65 %, obtained with rhodium nanoparticles entrapped in boehmite nanofibers as catalyst [13].

The preferred retrosynthetic route leads over **TM 2.5a** to the next generation TM **2.5b** by the addition of a double bond (FGA) at the proper position in the cyclohexane ring followed by *retro*-D.-A. disconnection (Scheme 2.10).



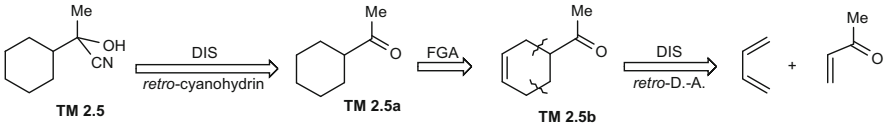
TM 2.5 **TM 2.5a**

Scheme 2.8 First retrosynthetic step for **TM 2.5**



TM 2.5b **TM 2.5a**

Scheme 2.9 Possible synthetic route to **TM 2.5a**



Scheme 2.10 Correct retrosynthetic analysis of **TM 2.5**

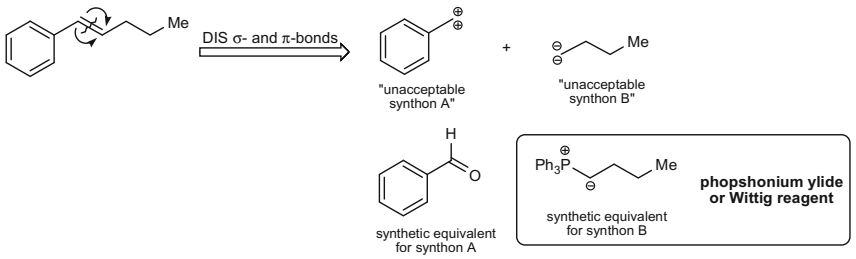
In the first step we perform *retro*-cyanohydrin disconnection, in the next step we add a double bond at the strategic position in the cyclohexane ring, and in the final step *retro*-D.-A. disconnection results in the easily available starting materials butadiene and methyl vinyl ketone.

2.3 Disconnection of Alkenes

In this section we shall closely inspect the retrosynthetic approach to simple alkenes, which includes disconnection of the C=C bond in two synthons, which have useful building blocks for synthetic equivalents. We shall not consider the formation of a double bond by β-elimination of two substituents on the vicinal carbon atoms, as for instance dehydration. More about these approaches is presented in the Sect. 4.3.1.

Double disconnection of the C=C bond can be formally presented as in Scheme 2.11.

The presented disconnection looks ugly, mechanistically incorrect and energetically unacceptable, generating synthons with double charges on the terminal C atoms. Having in mind that any disconnection is an imaginative process, we can start searching for proper reagents for such "unacceptable synthons". Surprisingly, it turns out that they exist! The reagent for "unacceptable synthon A" is benzaldehyde, where an electronegative oxygen atom donates two electron pairs to the C=O bond, compensating two formal positive charges in this synthon. To discover an acceptable reagent for "unacceptable synthon B" with a double negative charge on the terminal C atom helps another imaginative consideration. For an effective



Scheme 2.11 Formal presentation of double disconnection of the C=C bond

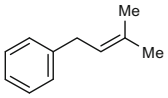
reaction with the carbonyl group, carbanion is needed as the second reagent; so one negative charge in this synthon serves the purpose. The second negative charge is compensated by delocalization bound to an electropositive atom. The atom of choice is the P atom and as a highly effective synthetic equivalent the *phosphonium ylide* or *Wittig reagent* emerges [14–16].

Note Ylides are neutral, dipolar molecules that comprise a C atom with a formal negative charge directly bound to the positively charged heteroatom, usually nitrogen, phosphor or sulfur. They are characterized by separated charges in the *betaine structure*. Both vicinal atoms possess an octet of electrons and can be regarded as 1,2-dipolar compounds [17].

Formation of the C=C bond enables the couple carbonyl compound-ylide as a nucleophile. An electron pair of carbanions in phosphonium ylide forms one of two C=C bonds with the carbonyl C atom; the second one is formed by an electron pair "hidden" in the P–C bond. Here a general scheme is presented for the reaction of carbonyl compounds with stabilized carbanions and ylides in the preparation of alkenes (Scheme 2.12).

In the next example disconnection of an alkene reveals some typical "pitfalls" when proposing a synthetic route based on seemingly acceptable retrosynthetic analysis.

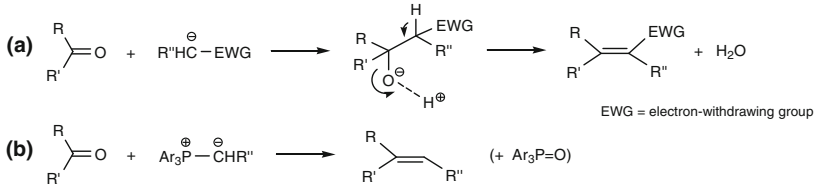
Example 2.6 Propose the retrosynthetic analysis and synthesis of **TM 2.6** without use of the Wittig reagent in the formation of the C=C bond.



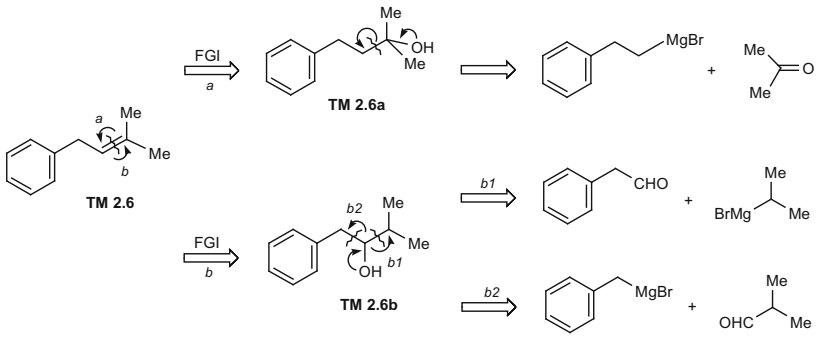
TM 2.6

Conceiving the formation of the C=C bond by the elimination of water, two possible FGIs in the first retrosynthetic step lead to two alcohols, **TM 2.6a** and **TM 2.6b**, as the targets of the second generation (Scheme 2.13).

FGI in step *a* opens a simple choice of which C–C bond in **TM 2.6a** to disconnect with the participation of the OH group. It results in the maximal simplification and two available reagents, acetone and the Grignard reagent, from 2-bromethylbenzene. FGI *b*, however, faces two possibilities for disconnection of the C–C bond in **TM 2.6b**, *b1* and *b2*. Both lead to one mole of aldehyde and one mole of Grignard reagent. Disconnection *b1* is unfavorable since Grignard reagent



Scheme 2.12 General schemes for **a** aldol condensation and **b** Wittig reaction

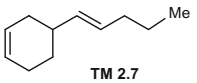


Scheme 2.13 Two possibilities in the retrosynthetic analysis of **TM 2.6**

needs to stabilize carbanion on the *sec* C atom destabilized by hyperconjugation. Disconnection *b2* leads to *iso*butyraldehyde, a large-scale industrial product available by the hydroformylation of propene catalyzed by Pt/Al_2O_3 (Sect. 3.1, Scheme 4.3). Grignard reagent derived from benzyl bromide is not a good choice because the carbanion on the benzylic C-atom is destabilized by resonance. Since the radical-anion on the benzylic C atom is less destabilized, Grignard reagent has a radical character and is prone to polymerization. Besides this argumentation against retrosynthetic consideration *b*, it should be noted that elimination of water toward the benzylic C atom competes with elimination toward the *tert*-C atom of the isopropyl group affording the structural isomer of **TM 2.6**. The origin of this competition resides in the similar C–H acidity of the two C atoms (kinetic argumentation) and comparable stabilization of the C=C bond by conjugation with the aromatic ring and by hyperconjugation with methyl groups (thermodynamic argumentation). For these reasons, the retrosynthetic route to **TM 2.6** over **TM 2.6a** is preferred.

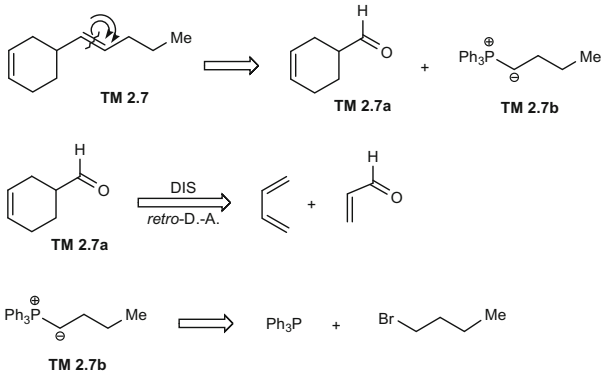
In the frame of the next example, we consider in more detail the mechanism and steric aspects of the Wittig reaction.

Example 2.7 Suggest the retrosynthetic analysis of **TM 2.7**, and then propose a synthetic route starting from the easily available Wittig reagent.



TM 2.7

The preferred double bond for disconnection is the one outside of the ring with an *E*-configuration. Disconnection of the ring will result in a formidable, branched-chain structure as a new TM! Note the position of the side chain relative to the C=C bond in the ring, suggesting the construction of cyclohexene by the Diels–Alder reaction with EWG in the side chain. *retro*-Wittig disconnection of the C=C bond in the side chain results in aldehyde **TM 2.7a** and Wittig reagent **TM 2.7b** (Scheme 2.14).



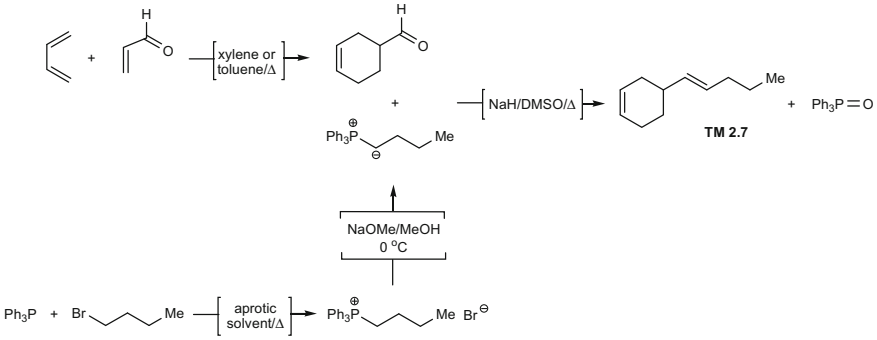
Scheme 2.14 Retrosynthetic analysis of **TM 2.7**

Target molecules of the next-generation **TM 2.7a** and **TM 2.7b** are easily available as demonstrated by the next retrosynthetic steps, the former by the Diels–Alder reaction from butadiene and acrolein (propenal) and the latter from 1-bromobutane and triphenylphosphine.

The proposed synthesis of **TM 2.7** is presented in Scheme 2.15.

On the formation of quaternary phosphonium salt by alkylation in aprotic solvent, deprotonation of C atom bound to a positively charged P atom is effected by the strong base. Phosphonium ylide reacts in the last step with aldehyde under heating in aprotic solvent to form **TM 2.7**. The most important aspect of the synthetic route in Scheme 2.15 is the stereoselective formation of the C=C bond with an *E*-configuration.

Note Let us see how this stereochemical outcome is controlled. Depending on the stability of phosphonium ylide in the Wittig reaction, formation of an *E* or *Z* isomer



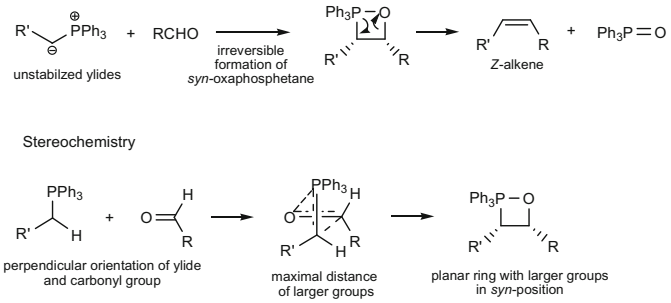
Scheme 2.15 Proposal for the synthesis of **TM 2.7**

prevails around the C=C bond. In other words, the *stability of ylides controls the stereoselective synthesis of alkenes* [18, 19].

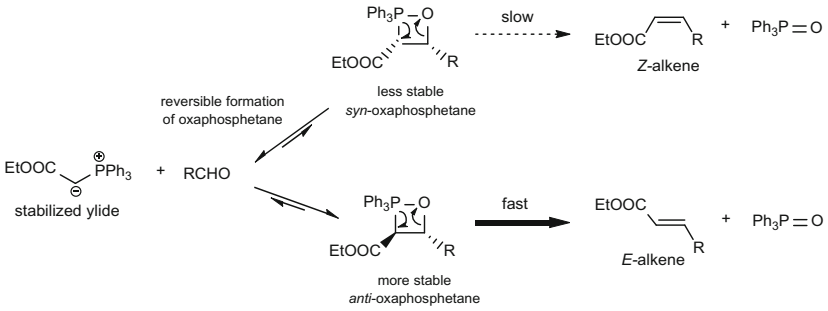
Stabilized ylides possess EWG on an α-C atom to the phosphonium group. Unstable ylides are avoided in EWG, and the carbanion is only stabilized by the phosphonium unit. *E/Z* stereoselectivity resides in a transitory formation of a four-membered oxaphosphetane ring whose structure is dependent on the stability of ylides (Schemes 2.16 and 2.17) [18].

Unstabilized ylide forms under kinetic control of *syn*-oxaphosphetane as the consequence of the perpendicular orientation of the ylide and carbonyl group, assuring the maximal distance of larger groups. From this intermediate, *Z*-alkene is formed (Scheme 2.16).

When stabilized ylide reacts, equilibrium of *syn*- and *anti*-oxaphosphetanes is formed, and in the fast step the *anti*-isomer reacts, affording thermodynamically more stable *E*-alkene (Scheme 2.17).



Scheme 2.16 Mechanism of the Wittig reaction with unstabilized ylide



Scheme 2.17 Mechanism of the Wittig reaction with stabilized ylide

2.3.1 *Examples of the Wittig Reaction on the Industrial Scale*

The question often arises about to what extent a certain synthetic reaction is technologically feasible on the large scale and acceptable from the perspective of environmental protection. The Wittig reaction is an excellent example for consideration of the above aspects in a synthetic reaction and for the introduction of criteria for evaluation.

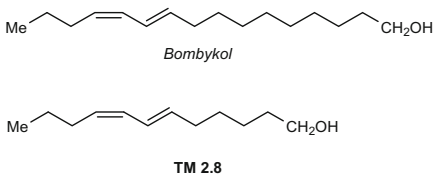
Besides the "atom economy" discussed in the Sect. 1.3, the feasibility of certain synthetic reactions on the large-scale is determined by other parameters, such as the price and availability of raw materials, solvents, catalysts, energy consumption and cost of equipment. Deposition of the waste and in particular the possibility for its economic recycling are decisive parameters.

Having in mind these aspects of large-scale syntheses, the question arises whether Wittig synthesis is acceptable as a large-scale production method in view of the low "atom economy," use of triphenylphosphine and formation of large quantities of triphenylphosphine oxide as a side product. To answer this question, we note that the low economy of atoms in this reaction is vastly compensated by the low-cost production of triphenylphosphine and elegant recycling of P-oxide on the large scale (Scheme 2.18).

In the production of triphenylphosphine the side products are sodium chloride and water in the catalytic recycling of phosphine oxide! These aspects greatly help to illustrate the environmental acceptability of the Wittig reaction.

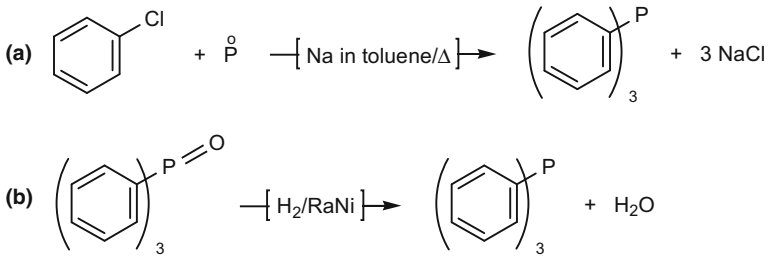
In view of the different steric outcomes of the Wittig reaction with two types of ylides, we consider some examples of this reaction in the commercial production of compounds with *E* or *Z* double bonds.

Example 2.8 The unsaturated C_{18} alcohol *bombykol* is a pheromone of the silkworm female. Suggest the synthesis of **TM 2.8**, the structural analog of *bombykol*, starting from phenol as the C_6 building block.



Bombykol

TM 2.8

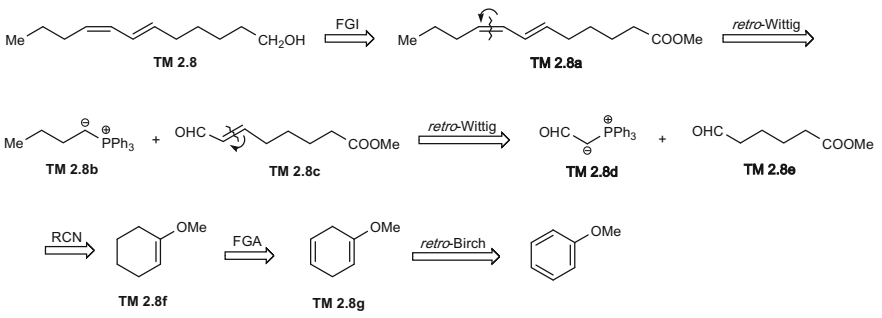


Scheme 2.18 Industrial method for the preparation and recycling of triphenylphosphine

We start retrosynthesis assuming that the terminal hydroxymethyl group in **TM 2.8** originates from phenol and so the six carbon atoms on the right side of the chain, including one in the *trans* C=C bond. This fragment obviously results in the opening of the aromatic ring. As we shall learn in Sect. 5.4 and 5.4.1, it requires two steps, Birch reduction to non-conjugated cyclohexadiene and selective ozonolysis of one C=C bond. Before reduction, the phenolic OH group is protected as methyl ether, which in the ozonolytic step becomes the COOMe group. Consequently, we can anticipate FGI of CH_2OH to COOMe in the first retrosynthetic step and propose methyl ester **TM 2.8a** as a TM of the next generation. The logical retrosynthetic assumption is also the reduction of the COOMe group in the last synthetic step. Now the dilemma arises of what double bond to disconnect first by the *retro*-Wittig, i.e., which one should be formed as the last in the synthesis. The principle of maximal simplification suggests disconnection of the C=C bond with an *E* configuration into two C_6 fragments. This disconnection results in alkene of a *Z* configuration formed from aldehyde and an *unstabilized ylide*. Now we follow a well-known principle in synthetic organic chemistry, the least stable functional group is introduced late in multistage synthesis. This principle suggests the formation of a *Z* double bond after a more stable *E* double bond, i.e., disconnection of the *E* double bond first.

These considerations suggest the retrosynthetic route outlined in Scheme 2.19.

A key point of the above retrosynthesis is the first *retro*-Wittig disconnection of **TM 2.8a** into unstabilized ylide **TM 2.8b** and conjugated aldehyde **TM 2.8c**. Inverse disconnection gives Wittig reagent with stabilized ylide on the allylic C atom, which will afford an *E* double bond instead of targeted *Z* bond. The second *retro*-Wittig disconnection of the *E* double bond in **TM 2.8c** results in stabilized ylide **TM 2.8d**. Therefore, two electron pairs are moved to C atom α- to the carbonyl group forming Wittig reagent **TM 2.8d**. The second reagent 1,6 dicarbonyl compound **TM 2.8e**, is *reconnected* into a derivate of cyclohexene **TM 2.8f**. In the synthetic direction ozonolysis of the C=C bond opens a ring in **TM 2.8f** affording 1,6-dicarbonyl structure **TM 2.8e**. On addition of the second C=C bond (FGA) to form non-conjugated cyclohexadiene **TM 2.8g** retrosynthesis brings us to the product of the Birch reduction from anisole.

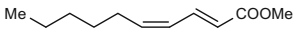


Scheme 2.19 Retrosynthetic analysis of **TM 2.8**

The proposed synthetic route to **TM 2.8** starts with anisole, which on methylation and Birch reduction affords a derivative of non-conjugated cyclohexadiene **TM 2.8g**. The importance and mechanism of this reaction are discussed in Sect.5.4. Chemoselective hydrogenation of one C=C bond is possible since the double bond in enol ether C=C–OMe is less reactive. **TM 2.8f** affords C_6 ester-aldehyde **TM 2.8e** on ozonolysis (Scheme 2.20).

The first Wittig reaction with stabilized ylide **TM 2.8d,** available from α-bromoacetaldehyde, affords conjugated *E*-alkene **TM 2.8c**. In the second Wittig reaction unstabilized ylide **TM 2.8b** forms a *Z* double bond in **TM 2.8a**. In the last step chemoselective reduction of the ester group to **TM 2.8** is completed with complex hydride.

Example 2.9 Ester with pear odor **TM 2.9** is an important product in the food and perfume industries. Complete its retrosynthesis and propose the synthesis.



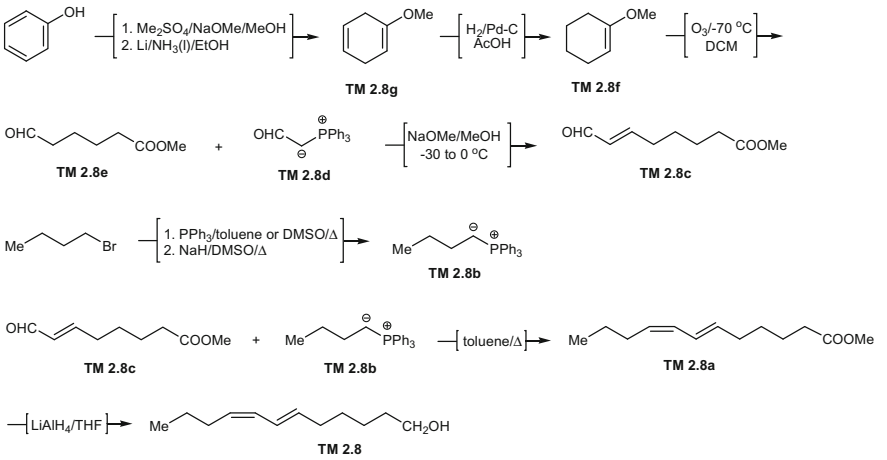
TM 2.9

As in the former example, here we meet a target molecule with conjugated *E,Z* double bonds. Therefore, a similar retrosynthetic consideration is proposed (Scheme 2.21).

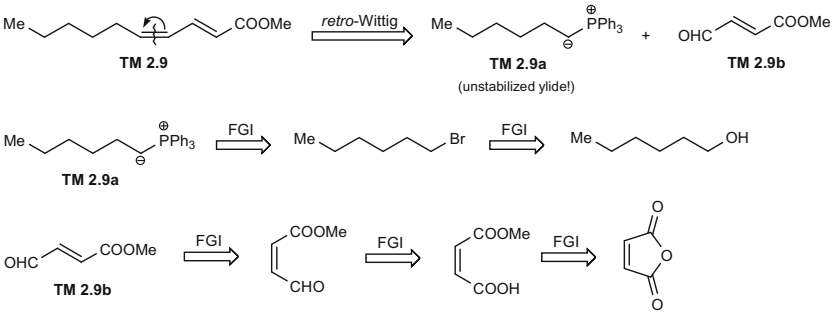
Unstabilized C_6 ylide **TM 2.9a** is available from 1-bromohexane, and this from *n*-hexanol (hexan-1-ol).

Note *n*-Hexanol is commodity produced catalytically by trimerization and hydration of ethylene (Scheme 2.22)

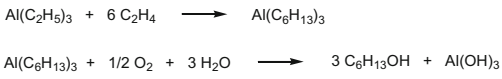
The limited quantities of oligomers formed are separated by fractional distillation of *n*-hexanol. Interestingly, this process competes with the fermentative production of *n*-hexanol from biomass, starch or cellulose. The third method for the production of *n*-hexanol is based on the hydrogenation caproic or *n*-hexanoic acid,



Scheme 2.20 Proposal for the synthesis of *bombykol* analog **TM 2.8**



Scheme 2.21 Retrosynthetic analysis of the odor principle of pear **TM 2.9**



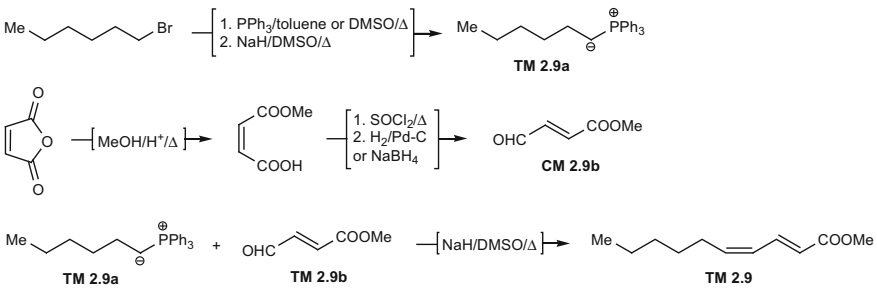
Scheme 2.22 Industrial method for the production of *n*-hexanol

available by the fermentation of glucose. Limited quantities of this acid are produced from diethylmalonate by alkylation with 1-bromobutane, followed by hydrolysis and decarboxylation.

To complete the retrosynthesis of the C_4 target molecule **TM 2.9b**, we need to take into account easy isomerization of the more available but unstable *Z* isomer to the stable *E* isomer. Then we can correlate the structure of **TM 2.9b** with maleic anhydride as the initial building block. Two FGIs interconvert the *Z* isomer of **TM 2.9b** into maleic anhydride.

Based on this retrosynthetic analysis, a workable synthetic route is proposed (Scheme 2.23)

A key step represents the chemoselective partial reduction of acid chloride from the monoester of maleic acid. This reduction can be completed to the level of aldhyde either catalytically or by complex hydrides. In the previous example we met the reagents and reaction conditions used in the final steps.



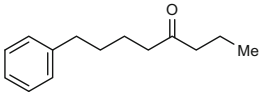
Scheme 2.23 Proposed synthesis of the odor principle of pear **TM 2.9**

2.4 Disconnection of Ketones

2.4.1 Disconnection of Dialkyl Ketones

In the introductory example (Sect. 1.3.1) we considered disconnection of **TM 1a** by *retro*-Friedel-Crafts and *retro*-Grignard. Both reactions are useful in the synthesis of aryl alkyl ketones of diverse complexity. In dialkyl ketones we consider the carbonyl group as directing the preferred C–C bond disconnection.

Example 2.10 Propose the retrosynthetic analysis for **TM 2.10** and suggest possible reagents.

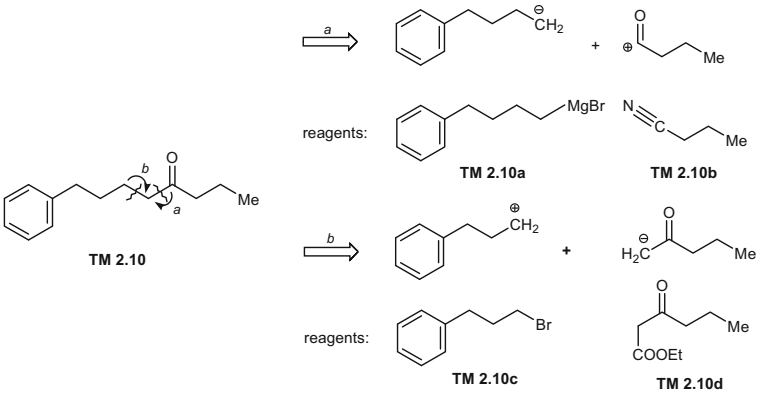


TM 2.10

Two plausible disconnections are presented in Scheme 2.24: (*a*) disconnection of the C–C bond between the α-C atom and carbonyl C atom and (*b*) disconnection of the C–C bond between the α- and β-C atoms to the carbonyl group. Both disconnections follow the principle of maximal simplification of the target molecule.

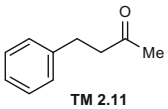
Synthons resulting from either disconnection have acceptable chemical species as reagents. We already met the disconnection of type *a* proposing retrosynthesis of **TM 1**. Disconnection *b* is based on a new concept, *introduction of an activating group*. Whereas carbocation has a logical reagent in 3-bromopropylbenezene **TM 2.10c**, carbanion cannot be selectively generated from pentan-2-one. Therefore, we conceive activating the carbethoxy group on the terminal α-C atom, enhancing its C–H acidity to pK_a ca. 11 and thus the stability of carbanion in **TM 2.10d**.

β-Keto acid **TM 2.10d** is not available; therefore, the synthetic route according to disconnection *a* is preferred. The reader should propose a synthetic route to **TM 2.10** considering the most effective approach to **TM 2.10a**.



Scheme 2.24 Preferred disconnections of dialkyl ketone **TM 2.10**

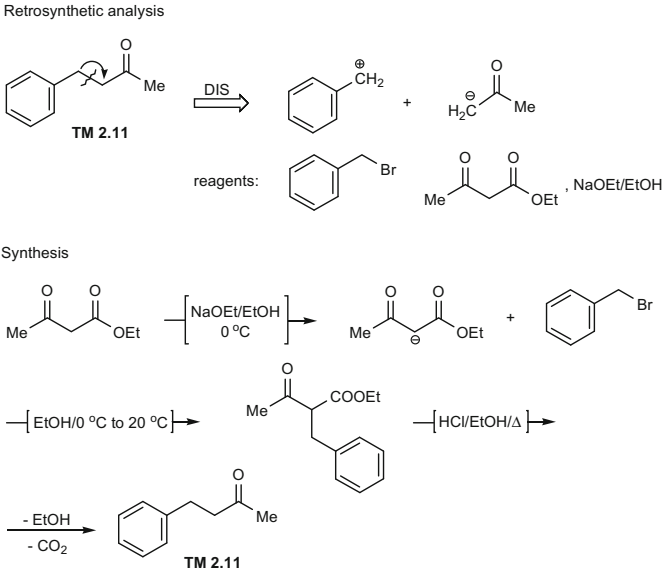
Example 2.11 Complete the retrosynthesis and propose the synthesis of benzyl acetone **TM 2.11**.



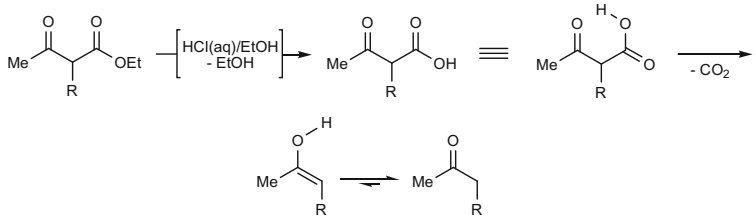
TM 2.11

In Scheme 2.25 retrosynthesis is proposed following previous argumentation for **TM 2.10**. Characteristic reaction conditions are given for the synthetic steps. Since pK_a of ethanol is 18 and pK_a of the methylenic group in acetoacetic ester is 11, deprotonation of **TM 2.10d** by sodium ethoxide is completely chemoselective. C-alkylation on the addition of benzyl bromide is followed by acidification and heating to complete the hydrolysis and decarboxylation to **TM 2.11**.

Note Activation of the C–H bond by the carbethoxy group in β-keto esters and its elimination by hydrolysis and decarboxylation, the last two steps in Scheme 2.25, deserve comment. The mechanism of decarboxylation is presented in Scheme 2.26.



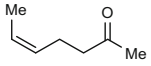
Scheme 2.25 Retrosynthetic analysis and proposed synthesis of benzyl acetone **TM 2.11**



Scheme 2.26 Mechanism of elimination of the activating carbethoxy group in β-keto esters

The key step represents elimination of CO_2 in the concerted process running over the six-membered transition state and is therefore energetically favorable. Easy and selective alkylation of the methylenic group in ethyl acetoacetate, the simple decarboxylation in the last steps and availability of this starting material make it the reagent of choice for acetonide carbanion. Ethyl acetoacetate is a commodity produced by the catalytic process discussed in connection with the retrosynthetic analysis of **TM 2.13**.

Example 2.12 Propose the retrosynthetic analysis of ketone **TM 2.12** taking into account the *Z* configuration of the double bond.

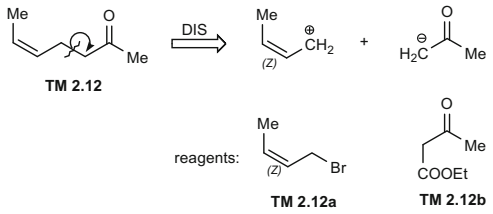


TM 2.12

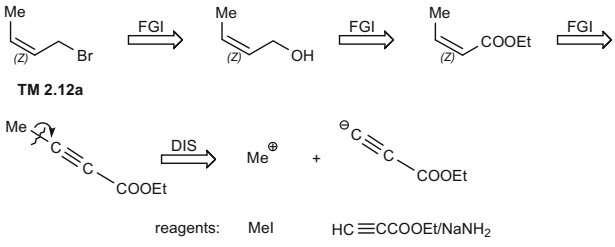
This example shows how retrosynthetic consideration of the next generation target molecules is sometimes more demanding than the choice in the first step. The logical first retrosynthetic step of **TM 2.12** is the disconnection of the C–C bond in the β position to the carbonyl group generating two stable synthons, carbanion on the α-C atom to the carbonyl group and carbocation on the α-C atom to the double bond, known as the *allylic cation* (Scheme 2.27).

Since the allyl cation is stabilized by resonance with the double bond, similar to the stabilization of the benzylic cation by an aromatic ring, the reactivity of the corresponding allyl halide 1-bromobut-2-ene **TM 2.12a** is enhanced, resembling that of benzyl bromide. The anionic C_3 synthon we already met in the former example will appear in many of the disconnections that follow.

Primary bromide **TM 2.12a** is easily available by bromination of primary alcohol and this in turn by reduction of the corresponding ester, as anticipated by the first two FGIs in Scheme 2.28.



Scheme 2.27 First disconnection step in the retrosynthesis of **TM 2.12**



Scheme 2.28 Retrosynthetic analysis of **TM 2.12**

The main synthetic issue on the route to **TM 2.12a** represents the introduction of the C=C bond to the *Z* configuration since products of most C=C bond-forming reactions possess a thermodynamically stable *E* configuration. Here we need new knowledge; the *triple bond can be selectively reduced to a double bond with Z configuration*.

Note Partial hydrogenation of the triple bond to the *Z* double bond is possible in the presence of *Lindlar catalyst*. This is a solid, heterogeneous catalyst based on Pd deposited on calcium carbonate and doped by various morphological forms of lead [20, 21]. Lead acts as a deactivator of palladium, and Pb(II) acetate and Pb(II) oxide also serve as "catalytic poisons." Since the addition of hydrogen on the triple bond occurs *syn*-selectively, the resulting alkene possesses a *Z* configuration of the double bond.

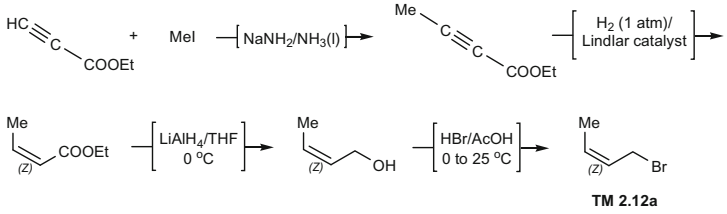
The second approach to the *Z* C=C bond offers the Wittig reaction with unstabilized ylide as discussed in the Sect. 2.2.2, but is a less attractive method for the large scale. Anticipating *Z*-selective hydrogenation of the triple bond, we propose a third FGI to the triple bond in ethyl butynoate and its disconnection to the methyl cation and anion of ethyl acrylate.

In summary, two interconversions of ally bromide afford allylic ester, followed by FGI of the *Z* double bond to triple bond and disconnection of C_4 alkyne to methyl halide and ethyl acrylate, both available reagents.

Based on this retrosynthetic analysis, the plausible synthetic scheme for **TM 2.12a** is proposed (Scheme 2.29).

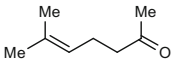
Methylation of the terminal acetylenic C atom requires deprotonation by strong bases since the pK_a of acetylene is ca. 25. *Z*-selective hydrogenation of the triple bond is followed by reduction to alcohol and bromination to **TM 12a**. In the last steps of synthesis, alkylation of ethyl acetoacetate **TM 2.12b** then decarboxylation as in Scheme 2.25 affords **TM 2.11**.

Example 2.13 Unsaturated ketone **TM 2.13** is the key intermediate in the industrial synthesis of β-carotene, a precursor of vitamin A. Start with the preferred disconnection of **TM 2.13**, continue the retrosynthesis to the reagent for the cationic

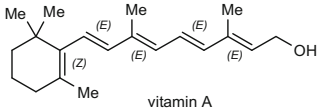


Scheme 2.29 Proposal for synthesis of **2.12a**

synthon and suggest the optimal reagent for the anionic synthon. Then propose the synthesis of **TM 2.13**.



TM 2.13



vitamin A

It is interesting to note that **TM 2.13** differs from **TM 2.12** by only one methyl group on the double bond; nevertheless, the preferred retrosynthetic analysis leads us to entirely different starting materials. As in Example 2.12, the first disconnection of the C–C bond in the α, β-position bond to the carbonyl group is preferred (Scheme 2.30).

The reagent for the allylic cation is the corresponding bromide **TM 2.13a**, a commodity with wide application in the fragrance industry. Its industrial synthesis, along with the industrial production of ethyl acetoacetate, is presented in Scheme 2.31. Both building blocks are used in the proposed synthesis of **TM 2.13**.

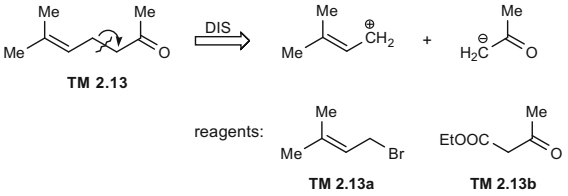
Starting from the petrochemicals acetylene and acetone, allylic carbinol is obtained by partial hydrogenation of the triple bond and brominated in the next step to **TM 2.13a**.

Note Here comes the important point; during bromination in the acidic medium, the intermediary allylic carbocation formed on the *tert*-C atom is in equilibrium with the more reactive *prim*-carbocation, which is brominated. This synthesis of 3,3-dimethylallyl bromide **TM 2.13a** is the basis of multi-ton industrial production since this compound is used in the agrochemical, pharmaceutical and dyestuff fields.

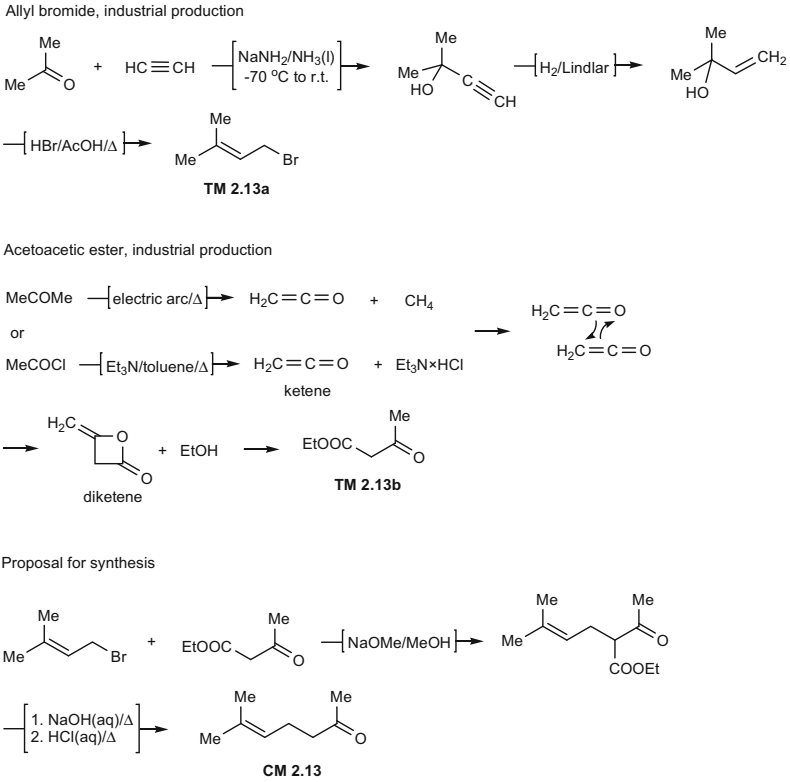
Two competitive methods are developed for the production of ethyl acetoacetate, both based on the dimerization of ketene (Scheme 2.31). By the first method, ketene is produced by thermal breakdown of acetone at over 300 °C [22], while the second "wet" method uses strong bases as catalysts for the elimination of hydrogen chloride from acetyl chloride [23]. Spontaneous dimerization results in a relatively stable four-membered lactone, known as diketene on the market, which on alcoholysis affords ethyl acetoacetate [24].

In the last steps of the proposed synthesis of **TM 2.13**, the alkylation of **TM 2.13b** and decarboxylation are completed according to the previously described protocol for **TM 2.11**.

Scheme 2.30 Retrosynthetic consideration of **TM 2.13**



TM 2.13 **TM 2.13a** **TM 2.13b**

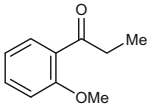


Scheme 2.31 Production of intermediates **TM 2.13a** and **TM 2.13b** and proposal for the synthesis of **TM 2.13**

2.4.2 *Disconnection of Alkyl Aryl Ketones and Diaryl Ketones*

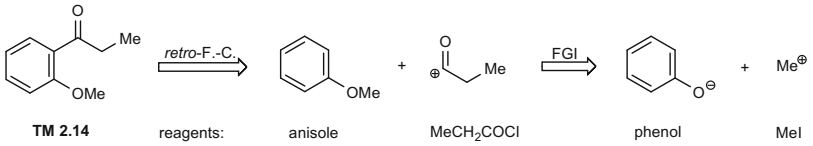
As mentioned in the introduction to this chapter, *retro*-Friedel-Crafts is the basic disconnection of the Ar–CO bond in alkyl-aryl ketones. Hereafter, we will discuss two examples where problems of regioselectivity in acylation and reactivity of the aromatic ring are tackled.

Example 2.14 Propose the retrosynthesis of **TM 2.14** and indicate the problem hidden in the synthetic direction.



TM 2.14

The logical first step is *retro*-F.-C. disconnection to anisole (methoxybenzene), a commodity available by the methylation of phenol (Scheme 2.32).

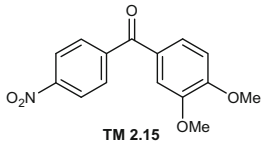


Scheme 2.32 Retrosynthetic analysis of **TM 2.14**

According to this retrosynthetic analysis, synthesis cannot be unambiguously completed. *ortho*-Acylation is sterically perturbed by the methoxy group, and an undesired *para*-isomer is prevalently formed (Scheme 2.33).

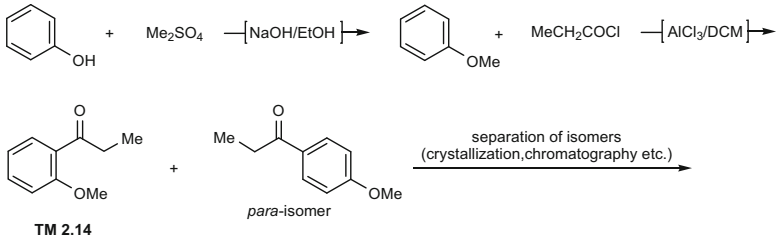
This issue can be solved by two approaches. The first is based on the separation of two structural isomers by known methods, primarily by selective crystallization or chromatographic separation on a preparative scale. The second introduces a *protecting group* to the *para*-position and eliminates it on completed acylation. In our example a good protecting group is chlorine. *para*-Chlorophenol is a commodity that is submitted to hydrogenolytic removal of chlorine on O-methylation and *ortho*-acylation using the Pt/C catalyst under controlled conditions.

Example 2.15 Propose the retrosynthesis of **TM 2.15**. Explain the preferred disconnection and solve the issue of regioselectivity in all synthetic steps.

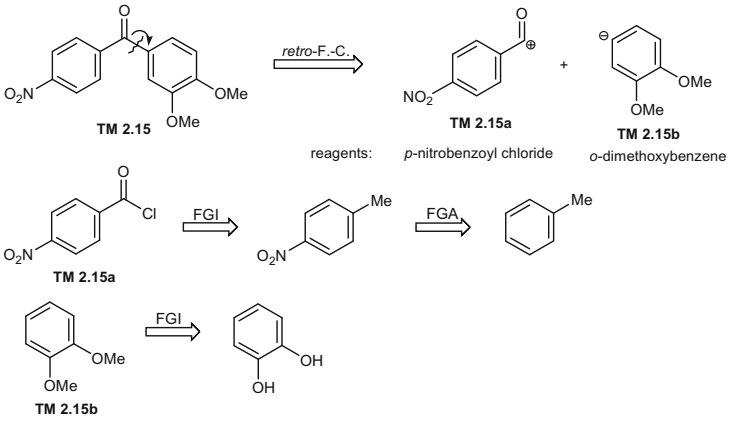


An obvious retrosynthetic step is *retro*-F.-C. disconnection, and the decision between two Ar-CO bonds is unambiguous in favor of the bond to the dimethoxyphenyl unit since this substrate is activated for F.-C. acylation (Scheme 2.34). Alternative disconnection leads to nitrobenzene, an unreactive aromatic compound in F.-C. acylation. Its high inertness enables its use as the solvent for this reaction!

The prevailing formation of *meta, para*-dimethoxy isomer **TM 2.15** is directed by steric perturbation at *ortho*-positions by methoxy groups.



Scheme 2.33 Proposed synthesis of **TM 2.14**

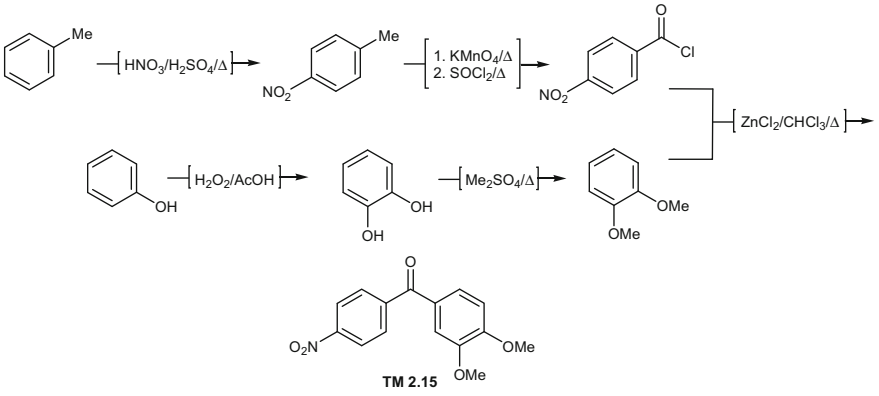


Scheme 2.34 Complete disconnection scheme for **TM 2.15**

Note Reagents for **TM 2.15a** and **2.15b** are available aromatic compounds, products of the petrochemical industry. *Para*-nitrobenzoic acid is produced by nitration of toluene to *para*-isomer as the prevailing product, followed by oxidation of methyl to the carboxylic group. *Ortho*-dimethoxybenzene is produced from *ortho*-diphenol, which in turn is available by oxidation of phenol. One technological process uses hydrogen peroxide as oxidant [25], and annual production of *ortho*-diphenol reaches 20,000 tons/year, mainly intended for the production of pesticides and perfumes.

Now we can propose the complete synthesis of **TM 2.15** (Scheme 2.35).

Note the parallel synthetic steps leading to key intermediates, which in the last step enter the F.-C. reaction affording **TM 2.15**. This is a general characteristic of *convergent syntheses* where two large building blocks are prepared separately and



Scheme 2.35 Proposal for the complete synthesis of **TM 2.15**

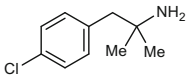
in the last step coupled into a final target molecule. Convergent synthesis reflects retrosynthesis where *maximal simplification* of the target molecule is performed in the first retrosynthetic step.

2.5 Interconversion of the Nitro Group, Nitroalkanes as Building Blocks

The amino and keto groups can be introduced in the target molecule in many different ways. The amino group is usually introduced by substitution of a good leaving group with nitrogen nucleophiles or by reduction of the imino or nitro group. The second approach is preferred since ammonia and amines are weak nitrogen nucleophiles. The keto group is most frequently introduced by oxidation of *sec* alcohols or by Grignard reaction as discussed in Sect. 1.3.1, Schemes 1.7 and 1.9.

With the next examples we introduce a new synthetic strategy for target molecules with oxygen and nitrogen functional groups. It is based on the use of building blocks with nitro groups available on the industrial scale by nitration of hydrocarbons. Reduction to the amino group or oxygenation to the keto group completes the approach to these functionalities.

Example 2.16 Consider the retrosynthesis of the anti-appetizer *chlorphentermine* **TM 2.16** and propose its synthesis.

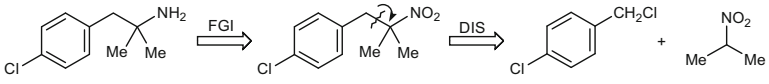


TM 2.16
Chlorphentermine

The presence of the Me_2CNH_2 group suggests the use of the Me_2CHNO_2 building block. Hence, in the first retrosynthetic step we propose FGI to the nitro group in **TM 2.16a** (Scheme 2.36).

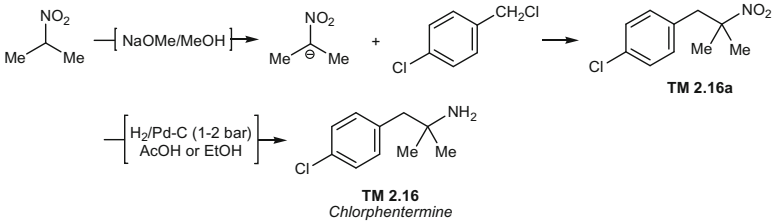
This is an appealing solution since disconnection of the central C–C bond in **TM 2.16a** results in stable synthons, benzyl cation and α-carbanion of 2-nitropropane. In the above scheme, the corresponding reagents are immediately presented and an unambiguous and short synthesis can be proposed (Scheme 2.37).

Importantly, in the scheme the generation of carbanion before the addition of benzyl chloride is indicated since the methoxy anion behaves as a competitive nucleophile. On completed alkylation, **TM 2.16a** is reduced chemoselectively



TM 2.16 **TM 2.16a**

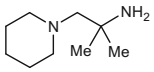
Scheme 2.36 Retrosynthesis of *chlorphentermine* **TM 2.16**



Scheme 2.37 Proposal for the synthesis of *chlorphentermine* **TM 2.16**

under controlled conditions affording **TM 2.16**. Higher hydrogen pressure or a larger ratio of the catalyst might cause the hydrogenolysis of chlorine.

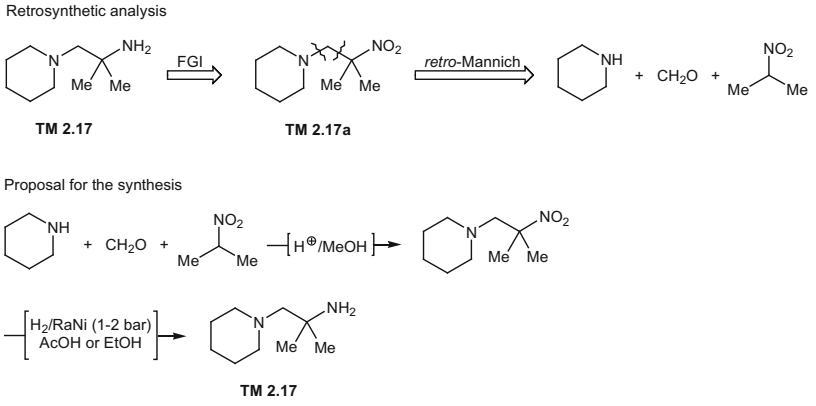
Example 2.17 Consider the retrosynthesis of diamine **TM 2.17**, a structural congener of **TM 2.16**, and propose a short synthesis.



TM 2.17

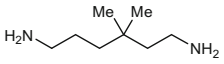
Again we have an amino group on the *tert*-C atom where it cannot be introduced by direct nucleophilic substitution. Therefore, the FGI of the amino to nitro group springs to mind (Scheme 2.38).

Disconnection of **TM 2.17a** requires new knowledge. This structure corresponds to the Mannich base since the *tert*-amino group is present in the β-position to the strong electron-withdrawing nitro group. The *retro*-Mannich type disconnection of two bonds leads to simple starting materials, piperidine, formaldehyde and 2-nitropropane. In the same scheme are proposed reaction conditions for the synthesis of **TM 2.17**. More details on the *Mannich reaction* are presented in Sects. 4.4.2 and 6.1. Here it suffices to mention that this *three-component reaction* affords β-amino carbonyl compounds known as *Mannich bases*.



Scheme 2.38 Retrosynthetic analysis and proposal for the synthesis of **TM 2.17**

Example 2.18 Complete the retrosynthetic analysis of C_8 diamine **TM 2.18**, an important monomer for the industrial production of polyamides, and suggest its three-step synthesis starting from easy available commodities, nitromethane, acrylonitrile and isobutyraldehyde.



TM 2.18

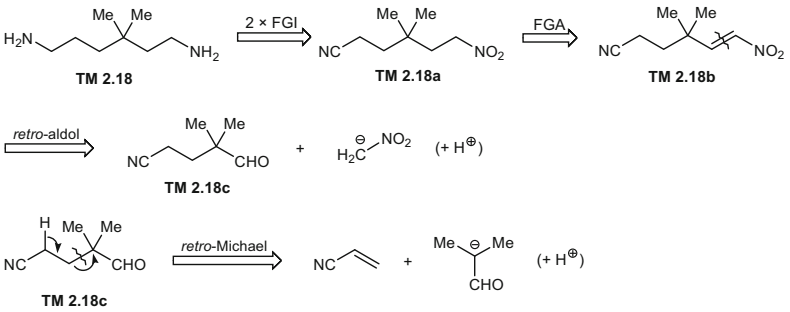
Obviously, both primary amino groups originate from the CN and NO_2 group in two building blocks. The next consideration requires more retrosynthetic skill. Since the CN group is incorporated as acrylonitrile, this C_3 building block is the origin of the amino group and three C atoms left from the quaternary one. Disconnection of the C–C(Me_2) bond requires the formation of carbanion on the *tert*-C atom of the Me_2C group and acrylonitrile as an electrophile. This reaction is known as the *Michael addition* of stable carbanions to enones as electrophiles and is discussed in more detail in Sect. 4.4. The amino group on the right side and terminal C atom obviously originate from nitromethane. The remaining C_4 unit at the branching point then belongs to isobutyraldehyde.

Having identified all building blocks in **TM 2.18,** we can propose retrosynthetic Scheme 2.39.

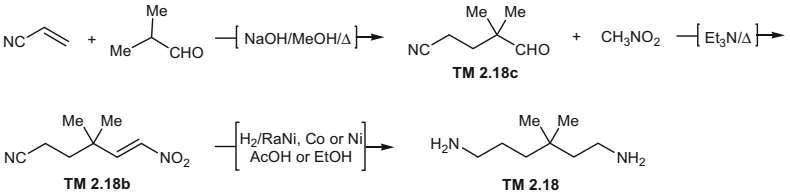
The first two FGIs interconvert two amino groups into their precursors in **TM 2.18a**; next FGA introduces the double C=C bond in **TM 2.18b**, enabling *retro*-aldol disconnection of nitromethane and **TM 2.18c**. Cyano-aldehyde **TM 2.18c** affords acrylonitrile and stabilized carbanion of isobutyraldehyde on *retro*-Michael disconnection.

According to this retrosynthetic consideration, the short synthesis of **TM 2.18** is proposed (Scheme 2.40).

The particular convenience of this three-step synthesis represents the *contemporaneous reduction* of the C=C bond and two nitrogen functionalities in the last step.

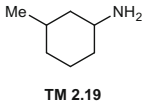


Scheme 2.39 Retrosynthetic analysis of **TM 2.18**



Scheme 2.40 Proposal for the synthesis 1,6-diamine **TM 2.18**

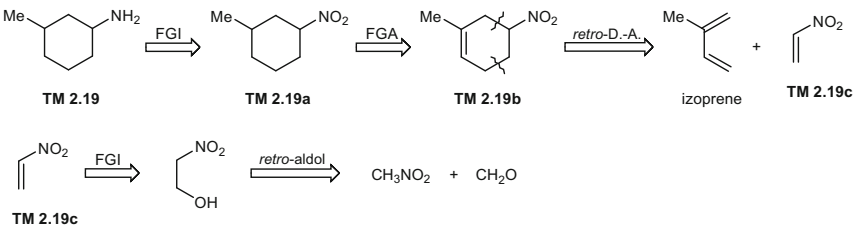
Example 2.19 Consider the synthesis of 1,3-disubstituted cyclohexane **TM 2.19** using C_5 diene as a strategic building block.



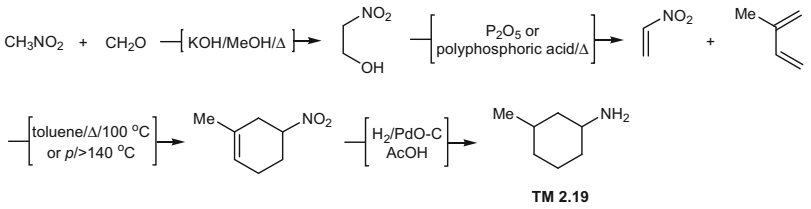
This information eliminates the cyclohexane derivative or its aromatic precursor as stating material. It also indicates the C_2 unit is the second building block and suggests the construction of a carbon skeleton by Diels–Alder reaction. Diene C_5 with a Me group is present in isoprene (2-methylbuta-1,3-diene). C_2 dienophile should be activated by EWG, and the nitro group serves this purpose best. This analysis suggests amino-nitro FGI to **TM 2.19a** as the target molecule of the next generation. By addition of the C=C bond in a strategic position on the cyclohexane ring, we arrive at key intermediate **TM 2.19b**. This cyclohexene derivative is now prone to r*etro*-D.-A. disconnection to isoprene and nitroethylene **TM 2.19c** (Scheme 2.41).

In spite of its relative instability nitroethylene (pure compound readily decomposes at r.t., but is stable in benzene solution over months!) is conveniently produced in kilo-quantities by dehydration of 2-nitroethanol according to the method outlined in the proposed synthesis of **TM 2.19** (Scheme 2.42) [26].

Note that **TM 2.19a** does not appear as an intermediate in the synthetic direction since both unsaturated functionalities in the product of the Diels–Alder reaction are contemporaneously reduced.

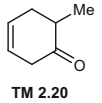


Scheme 2.41 Retrosynthetic analysis of **TM 2.19**



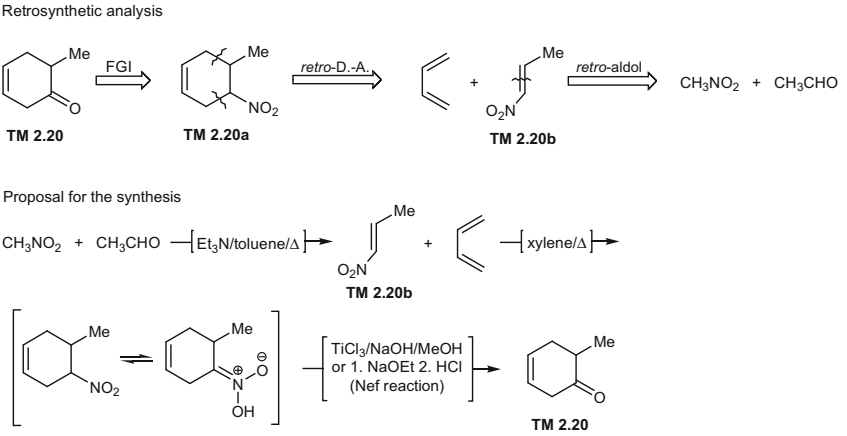
Scheme 2.42 Proposal for the synthesis of **TM 2.19**

Example 2.20 Propose the retrosynthetic analysis of non-conjugated cyclic enone **TM 2.20** and suggest the three-step synthesis.



The presence of a double bond and keto group in the cyclohexane ring indicates that the carbon framework is not available by partial hydrogenation of the benzene derivative. To solve the retrosynthetic puzzle, we need new knowledge. This rests in the possibility to transform a nitro to keto group by the oxygenation of the enolic form of the nitro group. The usual protocols use strong protic acids, the Nef reaction [27] or Lewis acids, preferably $TiCl_3$ [28]. Retrosynthetic analysis needs interconversion of the keto to nitro group in **TM 2.20a** in the first step, an imaginative FGI based on the above reaction (Scheme 2.43).

retro-Diels-Alder disconnection of **TM 2.20a** results in butadiene and 1-nitropropene as dienophile. *retro*-Aldol disconnection of **TM 2.20b** results in nitromethane and acetaldehyde. A proposal for the synthesis is given in the scheme, denoting the reactive form of the nitro group in the course of oxygenation.



Scheme 2.43 Retrosynthetic analysis and proposal for the synthesis of **TM 2.20**

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