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A Decision Tree for Retrosynthetic Analysis

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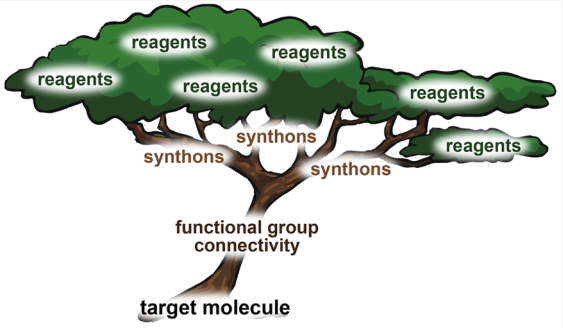
ABSTRACT: When organic students are asked to design a total synthesis of a molecule, they are often overwhelmed by the multitude of possible transformations. A decision tree is a useful tool to break complex problems up into simpler steps and scaffold the thinking process that many seasoned chemists take for granted. While many comprehensive resources present the logic and reaction strategies of retrosynthetic analysis, students still require scaffolded training in analyzing the functional group patterns of a molecule to arrive at the most prudent reaction. This work presents a 1-page flowchart that is readily implemented by undergraduates, organizes content, and ultimately helps students gain an appreciation for the more systematic aspects of retrosynthesis and organic synthesis more broadly.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Mnemonics/Rote Learning, Problem Solving/Decision Making, Synthesis*

Target-based chemical synthesis has been a major research enterprise for more than a century and is a key element of introductory organic chemistry courses. While many students relish the creative aspects of designing a synthetic strategy (there is typically no one correct answer), many students can struggle with where to begin. Synthetic design has been aided by the mental exercise of retrosynthetic analysis.[1] In many respects, retrosynthesis seeks to elevate synthetic design from a creative art into a more logical and systematic discipline. However, while seasoned chemists are adept at interpreting organic structures to recall how functional group patterns can arise and be interconverted into one another, novice students can experience cognitive overload when faced with the daunting avalanche of functional group interconversions while still learning to parse the symbols and representations of organic structures.[2−5] Alternatively, a decision tree[6−8] can help students break down a problem into more manageable chunks, providing them with a place to begin their synthetic plan.

The retrosynthetic decision tree presented in Figure 1 guides students through how to extract the relevant structural information from the molecular target and identify how the functional group patterns interrelate to one another. (1) Students first identify the C−C bond connectivity between functional groups. (2) Certain functional group patterns lend themselves to certain idealized reaction patterns, the synthons. (3) Finally, the scope of the retrosynthetic problem narrows down to a key set of synthons so that students can focus on identifying real reagents for the synthons identified in step 2 above (from this point, students can then continue to work retrosynthetically to make their reagents).

The decision tree organizes the disconnections into a single diagrammatic representation, providing students with a convenient study/learning aid, where the workflow of a decision tree creates a scaffolded approach for students to perceive the logic and systematic advantages of retrosynthesis. This aspect of the decision tree is distinct from many comprehensive resources in which the logic and reaction strategies of retrosynthetic analysis may be presented over an entire chapter, where the avalanche of information and possible reactions is what students find overwhelming. Students still require scaffolded training in analyzing the functional group patterns of a molecule to arrive at the most prudent reaction, where a simpler flowchart is more readily implemented by undergraduates.

The natural and umpolung synthons in the decision tree (Figure 1) are labeled as electron donor ($\mathbf{d}^{\#}$) or acceptor ($\mathbf{a}^{\#}$) according to their position relative to the carbon of the functional group. This nomenclature for synthons is common in retrosynthetic analysis. Interestingly, the origins of both the alternating polarity of the carbons as one moves away from the carbonyl as well as the naming convention can be traced back more than a century,[9,10] before retrosynthesis was even articulated.[1] Additionally, the decision tree is primarily concerned with carbonyl chemistry because the carbonyl is the most important and central functional group in organic chemistry and biochemistry and is the primary way of making carbon−carbon bonds during what is typically the second semester sequence of organic chemistry.

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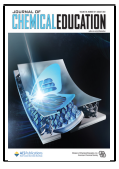

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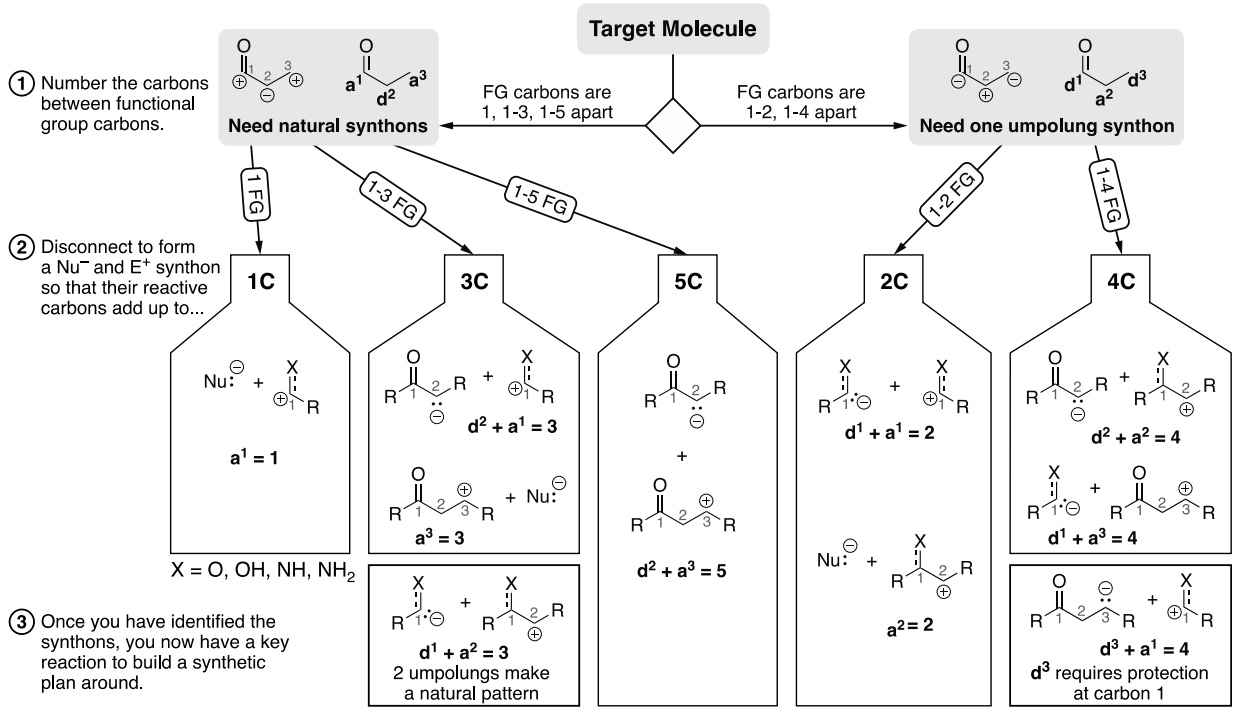


Figure 1. Decision tree to simplify retrosynthetic and forward synthetic analysis and planning. FG = functional group.

Table 1. Natural Synthons for 1, 1-3, 1-5 Functional Group Patterns

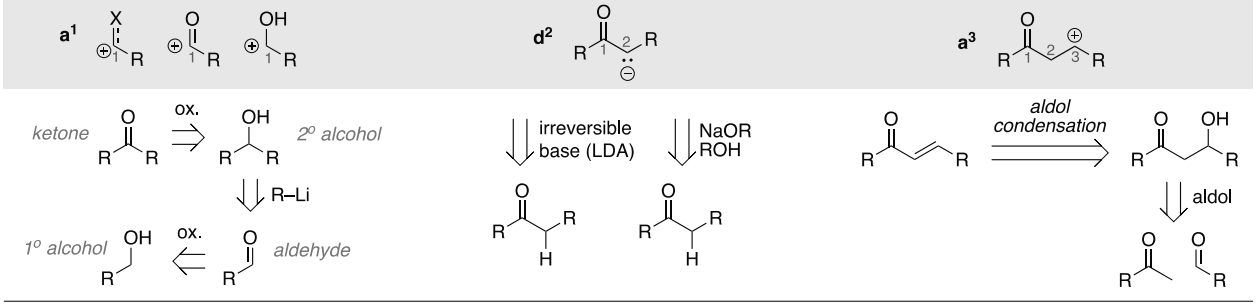
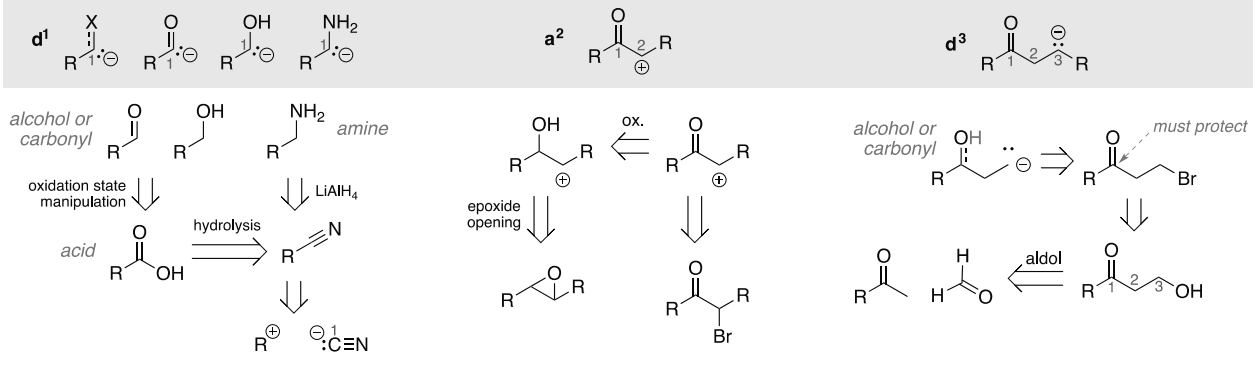


Table 2. Umpolung Synthons for 1-2 and 1-4 Functional Group Patterns



Students typically only require a few example problems to understand how to use the decision tree and understand that certain synthons are applicable to certain functional group patterns (see next section for examples). Alternatively, students can be encouraged to attempt a few problems on their own to discover how the decision tree provides a scaffolded approach to problem solving.[11,12] Many students enjoy the creativity inherent in deciding which disconnection to choose and the subsequent reactions that derive from that key reaction identified by the decision tree analysis. Alternatively, students can be given Tables 1 and 2 for a quick reference to how the synthons might be translated into actual synthetic reagents and/or steps for the forward synthesis. Tables 1 and 2 only catalogue a few of the common synthons for each acceptor/donor class to

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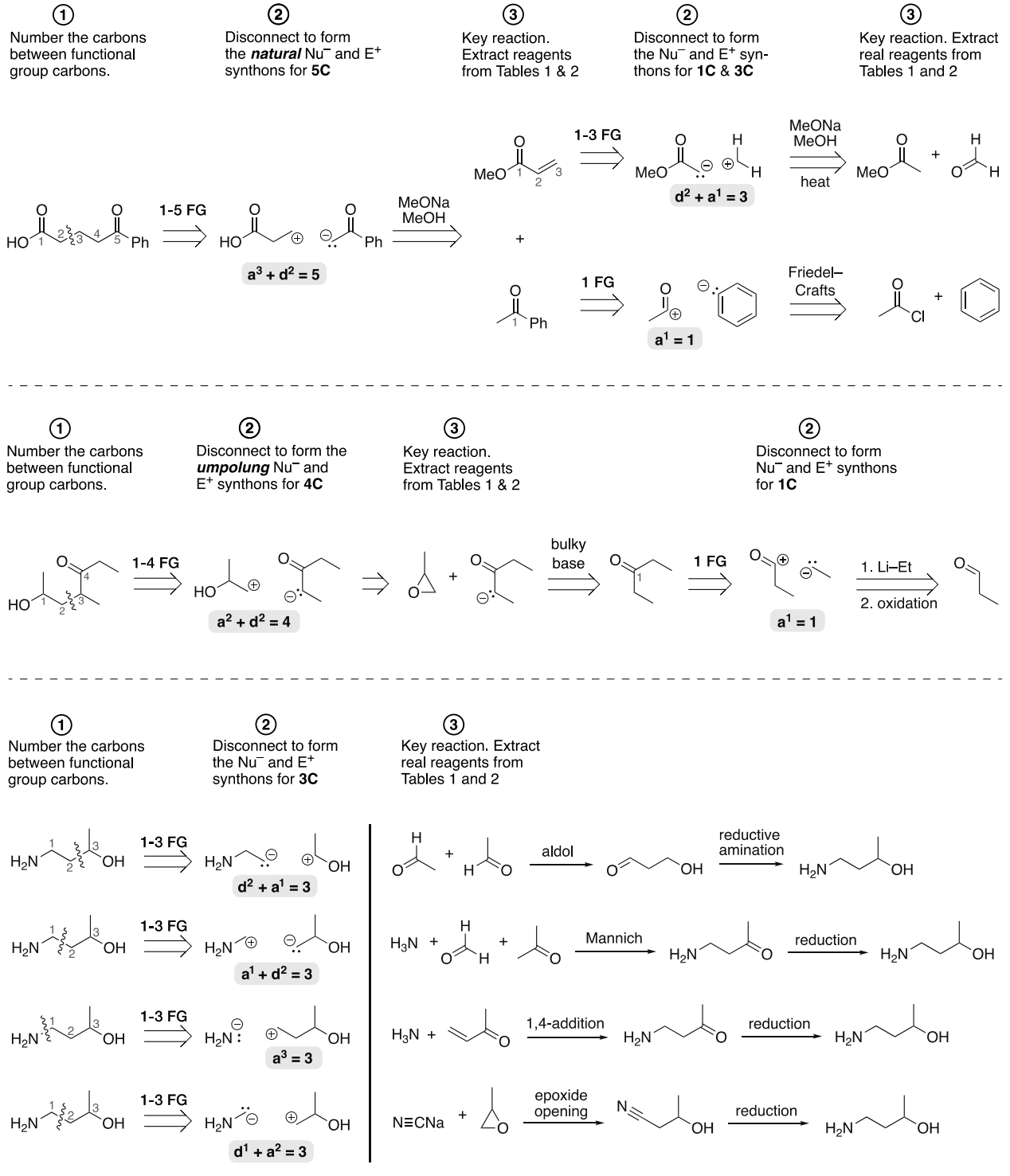

Figure 2. Example problems to teach students the workflow of the decision tree in Figure 1.

help students connect forward reactions with retrosynthetic disconnection steps. Both the inclusion of Tables 1 and 2, along with other reagents such as Wittig reagents or dithianes ($\mathbf{d^1}$), for example, could be easily supplemented at the discretion of the instructor and as the students develop mastery of the concepts.[13] Figure 1 and Tables 1 and 2 can serve as a 1-page reference sheet that students can consult while solving problems (see Supporting Information for reference sheets). Finally, the presence of an electrophilic and nucleophilic position within the $\mathbf{d^3}$ umpolung synthon provides a convenient opportunity to discuss protecting groups.[13]

■ EXAMPLE PROBLEM

A few examples are provided to showcase and introduce the workflow of the decision tree (Figure 2), which is formatted to also be easily given out to students. These examples highlight how the mental exercise of retrosynthetic analysis can be represented in a variety of ways (a combination of both retrosynthetic and forward synthetic arrows).[14] Once the basic

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concepts have been mastered, more complex retrosynthetic problems can be introduced.[15]

STUDENT FEEDBACK (ANONYMOUS SURVEY)

Students who had been given Figure 1 and Tables 1 and 2 as a 1-page reference sheet were given a slate of retrosynthetic problems as a part of a flipped-classroom problem-solving session.[12] Those students were later asked to respond to an optional anonymous survey. See SI for survey details and responses.

> *"The tree was especially helpful at the very beginning of the unit. I think that learning all of the synthons and how to make them would have been a lot more overwhelming and scarier without the tree breaking them down systematically."*
>
> *"I use it all the time! I definitely believe that some of the steps of the tree become second nature, and so I found myself using it less when I got more comfortable with the process. However, I would definitely recommend it to anyone who is completely lost about how to start."*
>
> *"It was great to be able to see what I needed after various tries. After looking at the decision tree enough, I could then just know which synthons were better than others to use."*
>
> *"Once I got more comfortable, I still would always check it to see if my synthons were correct so it at least gave me a level of confidence moving forward."*

SUMMARY

Retrosynthetic analysis is often described in terms of a tree, with the many varied and possible disconnections forming the different branches that all lead back to the target molecule.[16] The synthetic chemist must then choose the best path based on their "own qualifications and experience".[16] How can the novice chemist navigate the diverse branches of reagent sets, functional group interconversions, and bond connectivities? The decision tree described here, a fitting parallel to the analogy of the tree of retrosynthetic analysis, is proposed as a pedagogical tool to scaffold student thinking and problem solving for synthetic questions. Students have found that the decision tree for retrosynthetic analysis helps them to navigate the seemingly endless reaction possibilities of organic synthesis and gives them an organizational tool to more easily grasp both the content and concepts of retrosynthetic analysis. Future directions for this pedagogical tool will involve further quantitative data collection to illustrate the effectiveness of the decision tree.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.1c00447.

Single page reference sheets for all figures and tables (PDF)

Student survey details (PDF)

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Notes

The author declares no competing financial interest.

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