

Massachusetts Institute of Technology

Organic Chemistry 5.511

October 3, 2007
Prof. Rick L. Danheiser

Lecture 1: Strategies and Tactics in Organic Synthesis

Retrosynthetic Analysis

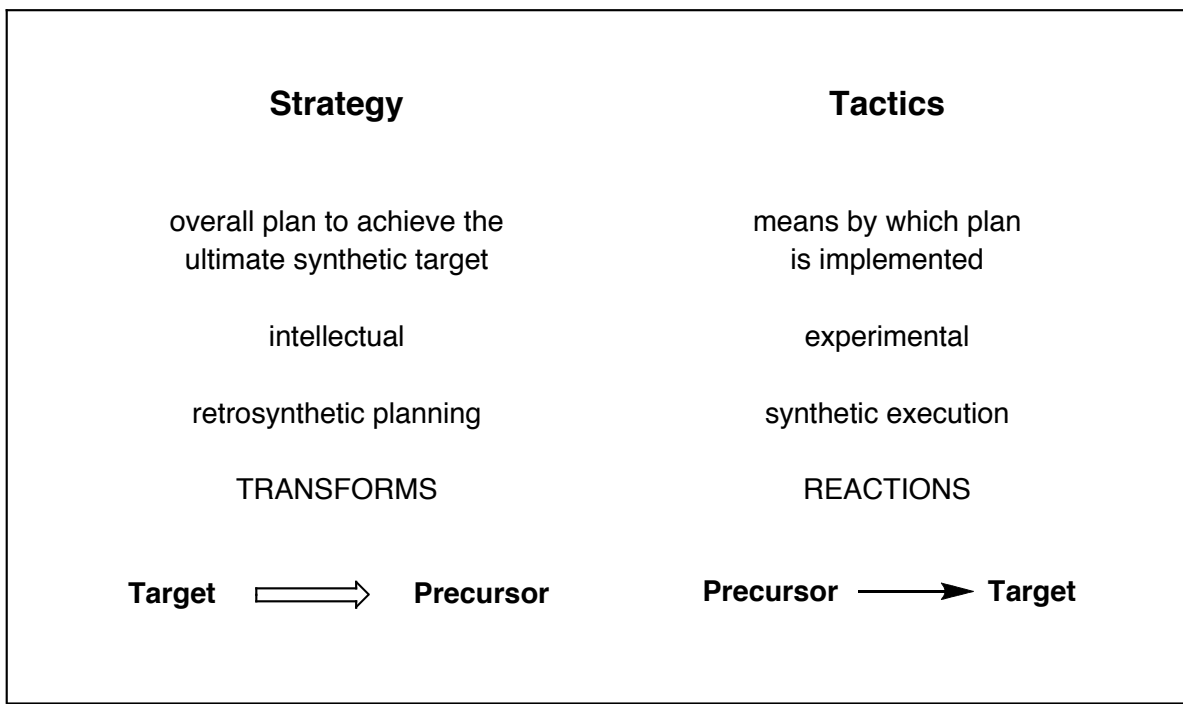
The key to the design of efficient syntheses

"The end is where we start from...."

T. S. Eliot, in "The Four Quartets"

"... the grand thing is to be able to reason backwards.
That is a very useful accomplishment, and a very easy
one, but people do not practice it much."

Sherlock Holmes, in "A Study in Scarlet"



Definitions

Retron

Structural unit that signals the application of a particular strategy algorithm during retrosynthetic analysis.

Transform

Imaginary retrosynthetic operation transforming a target molecule into a precursor molecule in a manner such that bond(s) can be reformed (or cleaved) by known or reasonable synthetic reactions.

Strategy Algorithm

Step-by-step instructions for performing a retrosynthetic operation.

"...even in the earliest stages of the process of simplification of a synthetic problem, the chemist must make use of a particular form of analysis which depends on the interplay between structural features that exist in the target molecule and the types of reactions or synthetic operations available from organic chemistry for the modification or assemblage of structural units. The synthetic chemist has learned by experience to recognize within a target molecule certain units which can be synthesized, modified, or joined by known or conceivable synthetic operations...it is convenient to have a term for such units; the term "**synthon**" is suggested. These are defined as structural units within a molecule which are related to possible synthetic operations... a synthon may be almost as large as the molecule or as small as a single hydrogen; the same atoms within a molecule may be constituents of several overlapping synthons..."

from "General Methods for the Construction of Complex Molecules"
E. J. Corey, *Pure Appl. Chem.* **1969**, 14, 19

"**Retron**: The minimal substructural element in a target structure which keys the direct application of a transform to generate a synthetic precursor."

from E. J. Corey and X.-M. Cheng,
"The Logic of Chemical Synthesis", 1989

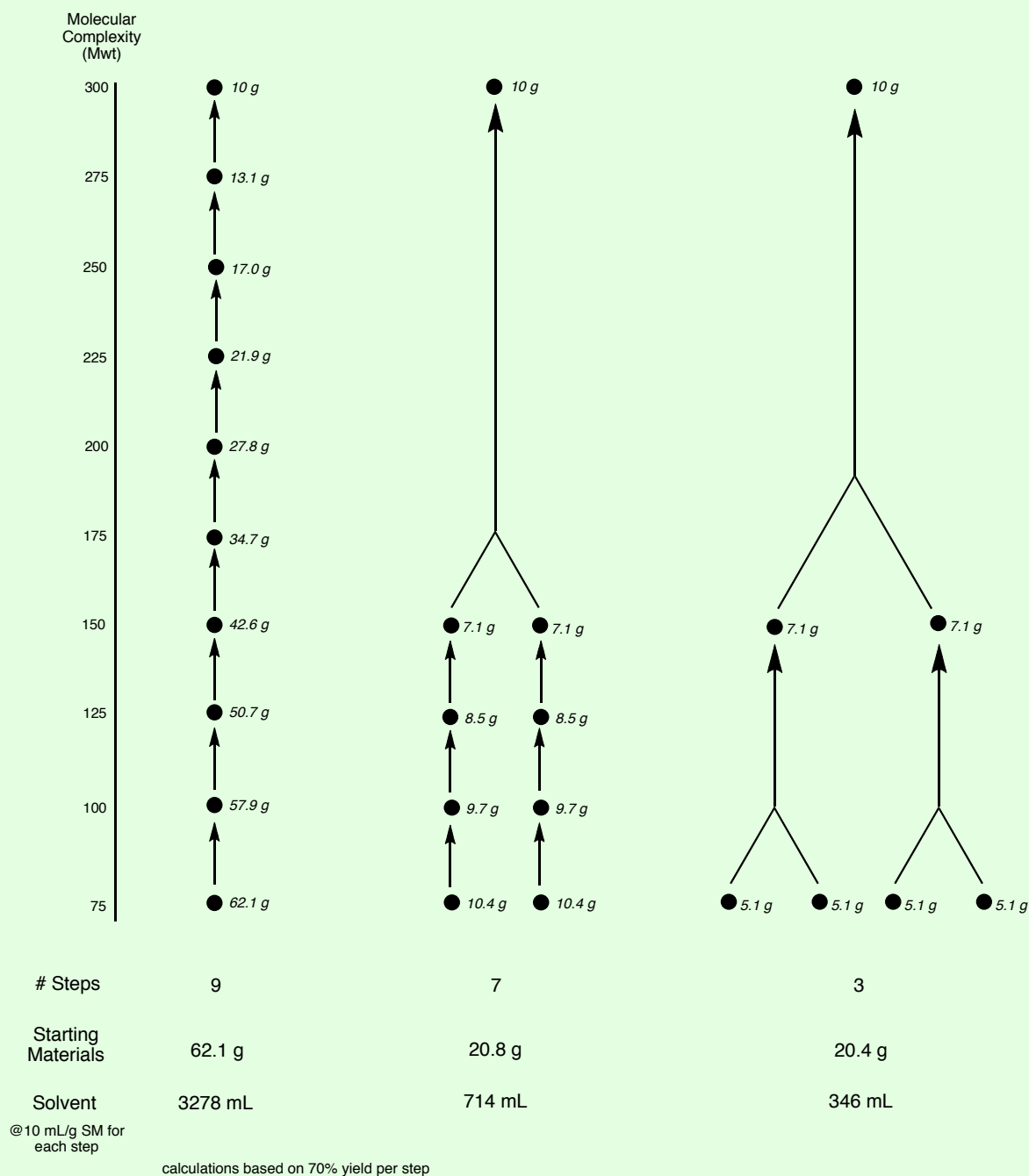


E. J. Corey

★ General Principles of Retrosynthetic Analysis ★

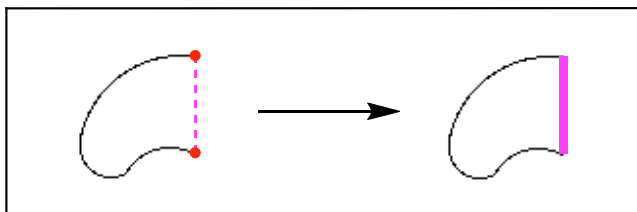
The first principle of retrosynthetic planning:
convergent strategies are the most
 efficient strategies for the assembly of
 complex molecules

The Power of Convergent Synthesis

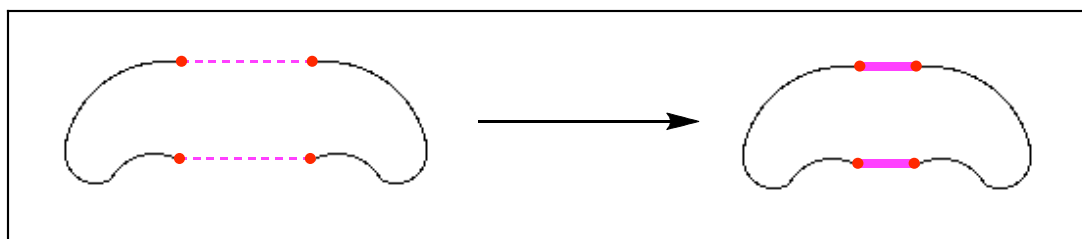


Strategies for the Assembly of Cyclic Compounds

Cyclization



Annulation

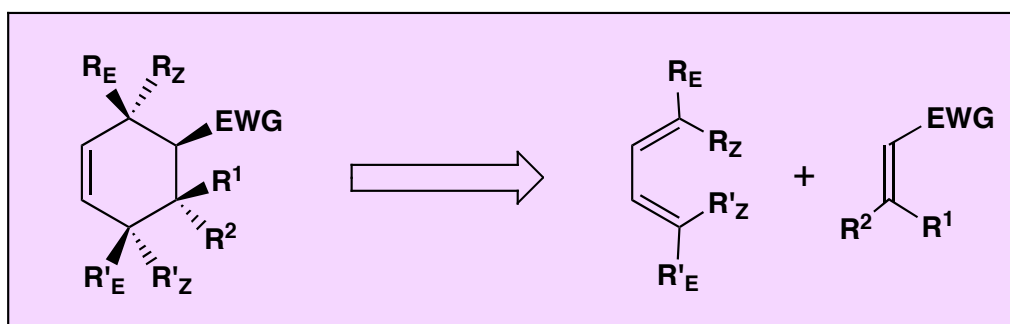


Concerted Cycloadditions

Non-Concerted "Single-Operation" Annulations

Multistep Annulation Strategies

The Diels–Alder Reaction



Otto Diels

Our results will play a role not only in the discussion of theoretically interesting questions . . . but probably also will yield greater significance in a practical sense. Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect. . . . We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems.

Otto Diels and Kurt Alder *Justus Liebigs Annalen der Chemie* **460**, 98 (1928)

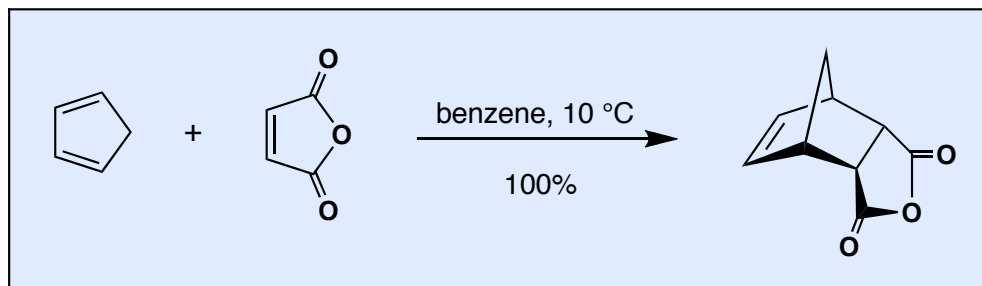


Kurt Alder

The Discovery of the Diels- Alder Reaction

"Tragt man in eine Suspension von 1 Mol. Maleinsäure-anhydrid in der 5 fachen Menge von reinem Benzol unter Kuhlung allmahlich 1 Mol. Cyclopentadien ein, so reagieren die Komponenten augenblicklich unter starker Warmentwicklung. Das Maleinsäure-anhydrid geht in Losung, und schon wahrend des Prozesses scheidet sich das Anhydrid der neuen Saure in schneeweissen, glanzenden Krystallen ab. Die Ausbeute ist nahezu quantitativ."

Otto Diels and Kurt Alder *Justus Liebigs Annalen der Chemie* **460**, 98 (1928)



Quote of the Day

*"I for one will not conceal my hope, contrary though it may be to the often too narrowly utilitarian spirit of the day, that synthesis for its own sake will continue. **There is excitement, adventure, and challenge, and there can be great art, in organic synthesis.** These alone should be enough, and organic chemistry will be sadder when none of its practitioners are responsive to these stimuli."*

R.B. Woodward in
"Perspectives in Organic Chemistry", 1956

