# 1.1: Introduction

The challenge of synthetic planning is the identification of a set of available precursors that can be combined and manipulated by a series of chemical reactions to provide the synthetic target. Analysis does not *a priori* have to proceed from target to starting materials along the exact reverse of the actual synthesis (i.e. **retrosynthetic analysis**), but this protocol is highly effective for the analysis of structurally complex molecules because it provides a logical basis for the systematic recognition of potential synthetic pathways. For example, recognizable characteristics of the precursors predispose them toward chemical reactions that generate the target. These characteristics are the result of certain structural features of the precursors (e.g. functionality), the residue of which is often apparent in the target and from which the precursor can be inferred. The ⇒ symbol is used to indicate one or more backward steps, often referred to as **dislocations** or **transforms** of the target to a precursor. Bonds severed in a dislocation (i.e. generated during the synthesis) are indicated by drawing wavy lines through the appropriate bonds. Furthermore, the target will generally be shown to the left of the ⇒ symbol and the precursor(s) to the right.The dislocation may correspond to a single known chemical reaction, or a hypothetical reaction, or may be the result of a multistep retrosynthetic process. For example, the hydroxyl group in a secondary alcohol may be viewed as the residue of the carbonyl functional group that predisposes a precursor aldehyde toward reaction with a Grignard reagent to deliver the synthetic target. The C=C bond in a cyclohexene may be viewed as the residue of the pi system in 1,3-butadienediene that predisposes this precursor toward a Diels-Alder cycloaddition with methyl acrylate to deliver the synthetic target.


The following dislocations of some molecules that we will consider more thoroughly in subsequent chapters show only the targets and a set of **starting materials**, precursors that are readily available organic chemicals. Thus, the overall strategy of each total synthesis is summarized in a single dislocation of the target. The molecular numbering system of the synthetic target is adopted to designate the corresponding atoms of synthetic precursors. The examples in Charts 1-3 provide a glimpse of the diversity of solutions possible for a particular synthetic problem. The systematic procedures which guide the invention of such strategies are the focus of this book.

Three overall strategies are presented in Chart 1 for the total synthesis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) a fatty acid derivative. These examples constitute a tiny sample of the numerous strategies that have been applied to the total synthesis of this important natural product.[1] These and other syntheses of prostaglandins will be considered in detail in chapter 3. Each strategy in chart 1 uses the same starting material **1** for carbons 1-5 of the upper side chain and similar starting materials **2** or **3** for carbons 14-20 of the lower side chain. But very different precursors are employed for the C6-7 and C8-13 portions of the target. Thus, the Woodward strategy involves ring contraction of a six- membered ring to generate the cyclopentane of C8-12 with C13 appended and glyoxalic acid to provide carbons 7 and 8.[2] The Brown strategy[3] uses α-chloroacrylonitrile for these carbons and acetoxyfulvene as precursor for the portion of the target which is provided by cyclohexanetriol in the Woodward synthesis. Turner's strategy carves the cyclopentane nucleus, C8-12, from the readily available Diels-Alder dimer of cyclopentadiene.[4] Thus, carbons 9-11 are derived from one molecule of cyclopentadiene while carbons 6-8 and 12-13 are derived from a second molecule of cyclopentadiene.

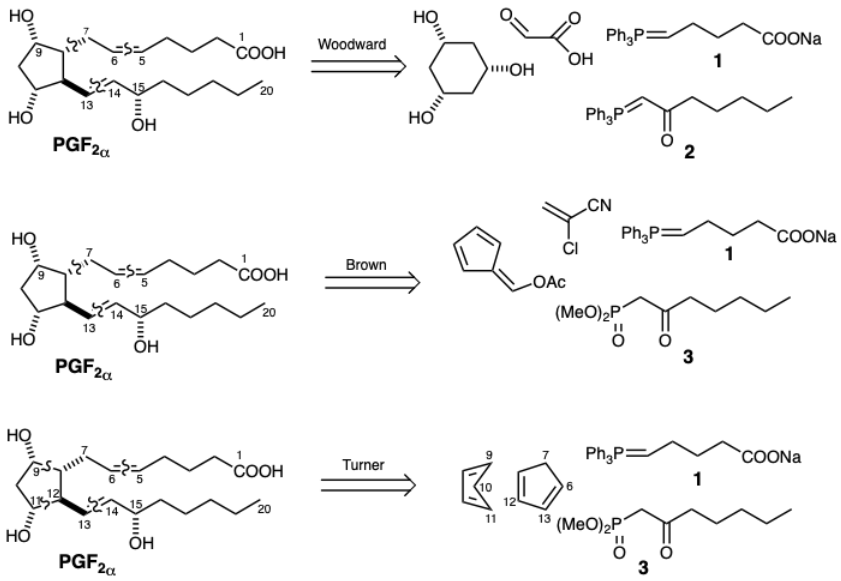


**Chart 1. Three Overall Strategies for Prostaglandin $F_{2\alpha}$**

Two strategies for total synthesis of the sesquiterpene longifolene are presented in Chart 2. The Corey synthesis[5] builds the tetracyclic skeleton from a cyclohexan-1,3-dione precursor that provides carbons 1 and 7-11. The Johnson strategy[6] builds the same carbon network from a cyclopentane precursor that provides carbons 1-3 and 9-11 of the target. The bonds formed in the two approaches are completely different.

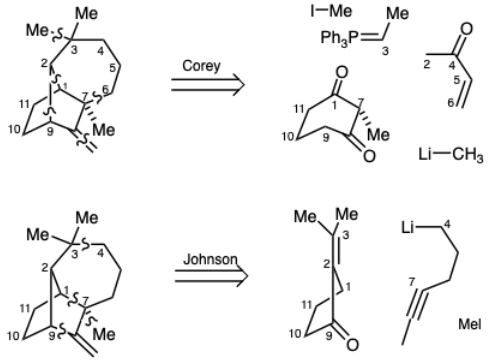


**Chart 2. Two Overall Synthetic Strategies for Longifolene**

While the choices of starting materials in the above examples may seem mysterious, consider the even more remarkable strategy for synthesis of these molecules in nature. As summarized in Chart 3, all of the carbon atoms of all natural products are derived from the same starting material, carbon dioxide. The biosynthesis of more complex biosynthetic building blocks, e. g., 3-phospho-D-glyceric acid and D-glucose from $CO_2$ will be our starting point for examining the logic that can be applied to designing total syntheses of organic molecules. The biosynthesis of natural products is a convenient framework for a systematic overview of the total synthesis of a variety of organic structural types. The logic of each biosynthesis will be considered and then compared with strategies employed in laboratory total syntheses of the same natural product.

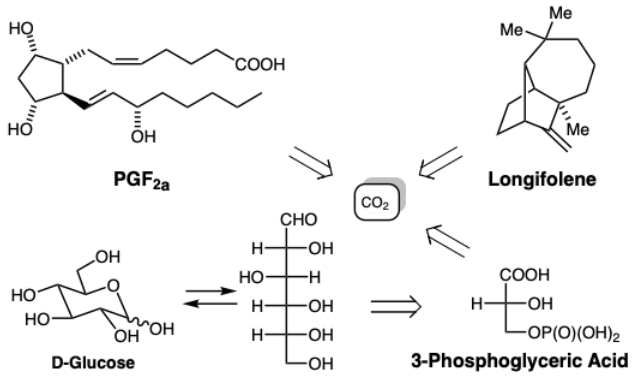


**Chart 3. The Common Feature of Biosynthetic Strategies: Start with $CO_2$**

First, however, in the remaining sections of this chapter, some basic principals of synthetic planning will be presented. The biosynthesis of glucose and other sugars from carbon dioxide in the dark reactions of photosynthesis will be examined in chapter 2. Sugars are not skeletally complex synthetic targets, but their functional and stereochemical complexity is a significant challenge for synthetic design. Chapter 2 concludes with a brief consideration of enantioselective total synthesis of sugars. Ensuing chapters examine the logic of biosyntheses and corresponding total syntheses of structurally complex natural products of the fatty acid, terpenoid, polyketide, and alkaloid families. An important feature of the discussion is the inclusion of unsuccessful plans that emerged from the work of leading practitioners of the art and science of organic total synthesis. These examples emphasize the practical limits of synthetic planning even by experts in the field.

Some previous books on the principles, logic, strategies, and tactics of synthesis design and surveys of total syntheses of complex organic molecules are described briefly in the following list.

A. A. Akhrem, A. A. Titov, A. Yu, *Total Steroid Synthesis* (Plenum, New York, NY, 1970): briefly discusses some principles of total synthesis and then exhaustively outlines total syntheses of steroids oganized according to topological categories of skeletal construction.

N. Anand, J. S. Bindra, and S. Ranganathan, *Art in Organic Synthesis* (Holden-Day, Inc., San Francisco, first edition, 1970): flow chart presentations of syntheses of complex organic molecules occaisionaly accompanied by brief discussions of strategic highlights.

N. Anand, J. S. Bindra, and S. Ranganathan, *Art in Organic Synthesis* (John Wiley, New York, second edition, 1987): updated flow chart presentations of syntheses of complex organic molecules occaisionaly accompanied by brief discussions of strategic highlights.

John ApSimon, Ed., *The Total Synthesis of Natural Products*, Vols. 1-9 (John Wiley & Sons, New York, 1973-1992): A collection of graphical surveys organized by biosynthetic families.

J. S. Bindra and R. Bindra, *Creativity in Organic Synthesis* (Academic Press, Inc., New York, 1975):

R. T. Blickenstaff, A. C. Gosh, G. C. Wolf, *Organic Chemistry Vol. 30: Total Synthesis of Steroids* (Academic Press, New York, 1974): exhaustively outlines total syntheses of steroids oganized according to topological categories of skeletal construction.

E. J. Corey and Xue-Min Cheng, *The Logic of Chemical Synthesis* (John Wiley & Sons, New York, 1989): duscusses the principles of synthetic design then provides specific examples by an exhaustive presentation of Corey's successful syntheses in outline format with little or no discussion.

Samuel E. Danishefsky and S. Danishefsky, *Progress in Total Synthesis* (Appleton-Century-Crofts, New York, 1971): graphical outlines of total syntheses of natural products organized by biogenetic families accompanied by a discussion of strategic highlights.

Ian Fleming, *Selected Organic Syntheses* (Wiley-Interscience, New York, 1973): discusses the key reactions in the total syntheses of more than two dozen complex organic molecules, the majority being natural products. It features multiple syntheses of several molecules, i. e. Cecropia Juvenile Hormone and Colchicine, providing an opportunity for comparison of different approaches.

J. Furhop, G. Penzlin, *Organic Synthesis. Concepts, Methods, Starting Materials* (Verlag Chemie: Weinheim, Fed. Rep. Ger., 1983): exhaustive systematic discussion of synthetic methods organized by synthons, difunctional relationships, and functional

group interconversions followed by a consideration of the principles of retrosynthetic analysis and graphical summaries for syntheses of a wide variety of complex organic molecules.

S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach* (Pergamon Press, London, 1983): concepts for designing total syntheses of natural products using readily available chiral nonracemic natural products as starting materials are discussed and extensively illustrated with examples.

Robert E. Ireland, *Organic Synthesis* (Prentice-Hall, Englewood Cliffs, New Jersy, 1969): A discussion of the principles of synthetic design is followed by a detailed consideration of specific examples of successful syntheses.

Thomas Lindberg, Ed., *Strategies and Tactics in Orgainc Synthesis*, Vols. 1-3 (Academic Press, Inc., New York, 1984-1991): anecdotal case histories of specific total syntheses illustrating the design and execution of synthetic plans and revealing the obstacles and failures commonly encountered even by experts.

Bradford P. Mundy, *Concepts of Organic Synthesis* (Marcel Dekker, New York, 1979): a review of synthetic methods organized according to specific goals or reaction types such as ring formation or rearrangements respectively. Also discussed are the biosynthesis of terpenes, concepts of stereocontrol and synthetic planning, and examples of complex syntheses.

Koji Nakanishi, Toshio Goto, Shô Itô, Shinsaku Natori, Shigeo Nozoe, Eds., *Natural Products Chemistry*, Vols 1-3 (Academic Press, Inc., New York, 1974-1983): information on the structural characterization and outlines of total syntheses organized by biogenetic families.

Fèlix Serrratosa, *Studies in Organic Chemistry 41*, *Organic Chemistry in Action The Design of Organic Synthesis* (Elsevier, Amsterdam, 1990): a textbook on the principles of synthesis design including the use of computers that concludes with several examples including several strategically different syntheses of twistane and lucidulene.

Stephen Turner, *The Design of Organic Synthesis* (Elsevier, New York, 1976): systematically discusses principles of synthesis planning with examples of considerable complexity. The focus is on concepts, and thorough discussion of specific total syntheses is not provided.

Stuart Warren, *Organic Synthesis: The Disconnection Approach* (John Wiley & Sons, New York, 1982): presents principles of synthesis planning on a very simple level. Concepts, especially retrosynthetic analysis, are defined and their applications systematically exemplified by the design of short syntheses of simple targets.


1. For a recent monograph, see: "New Synthetic Routes to Prostaglandins and Thromboxanes", Roberts, S.M.; Scheinmann, F., Academic Press, New York (1982).

2. Woodward, R.B.; Gosteli, J.; Ernest, I.; Friary, R.J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J.K. *J. Am. Chem. Soc.* **1973**, *95*, 6853.

3. Brown, E.D.; Lilley, T.J. *Chem. Commun.* **1975**, *39*.

4. Brewster, D.; Myers, M.; Ormerod, J.; Other, P.; Smith, A.C.B.; Spinner, M.E.; Turner, S. *J. Chem. Soc. Perkin I*, **1973**, 2796.

5. Corey, E.J.; Ohno, M.; Vatakencherry, P.A.; Mitra, R.B. *J. Am. Chem. Soc.* **1964**, *86*, 478.

6. Volkmann, R.A.; Andrews, G.C.; Johnson, W.S. *J. Am. Chem. Soc.* **1973**, *97*, 4777.