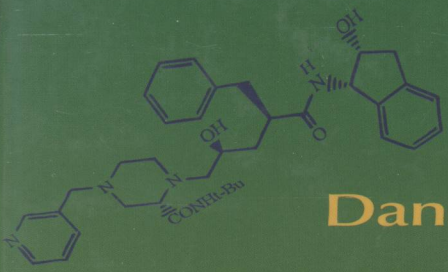
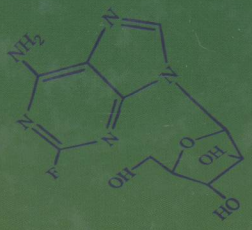
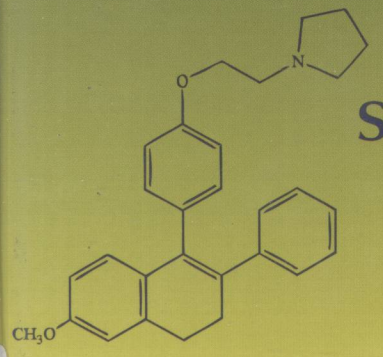


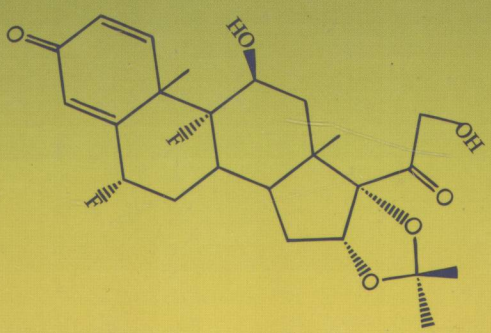


Daniel Lednicer

Strategies for Organic Drug Synthesis and Design

Second Edition





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STRATEGIES FOR ORGANIC DRUG SYNTHESIS AND DESIGN

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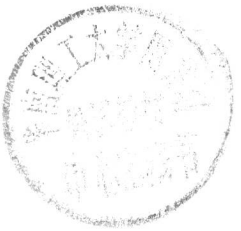

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STRATEGIES FOR ORGANIC DRUG SYNTHESIS AND DESIGN

To the memory of now-defunct laboratories where once I practiced my craft: Building H at G.D. Searle in Skokie, Upjohn's Building 25 in Kalamazoo and the diminutive Chemistry Annex at the Adria Laboratories just outside Dublin, Ohio.

PREFACE

"One of the most interesting aspects of organic chemistry is that of dealing with the building-up of complex substances from simpler ones. The synthesis of organic compounds, whether for scientific or industrial purposes, has been very important in the development of the science and is still of great importance today."

Those words, set down 80 years ago as the opening for a chapter on organic synthesis in Conant's pioneering textbook *Organic Chemistry*,* still very aptly describes the important role held by that aspect of the discipline. The use of organic transformations for the preparation of compounds with more or less complex structures has had a profound influence on both organic chemistry and, more importantly, on modern civilization. One need only bring to mind medicinal agents at one extreme and, on the other, the monomers used for the plethora of polymers that have provided the basis for a whole new materials science. The practice of organic synthesis covers an extremely broad range, from the highly practical, economically driven preparation of a tonnage chemical to a multistep, very elegant enantiospecific synthesis of a complex natural product. This very diversity may account for the relative paucity of books devoted specifically to the subject.

The manipulation used for the preparation of therapeutic agents seems to offer a middle ground between those extremes in complexity. The published syntheses for these agents are typically relatively short, seldom exceeding 10 or so steps. The target compounds for these syntheses do, however, cover a very wide range of structural types, encompassing both carbocyclic and heterocyclic compounds. The chemistry moreover includes a very broad selection of organic reactions. The published syntheses most often describe the route that was used in the discovery of

*Conant, James B.; *Organic Chemistry*, Macmillan, New York, 1928, p. 117.

some new compound. Some exotic and versatile reagents are used since reaction conditions are not circumscribed by their applicability to plant processes. The syntheses of therapeutic agents thus offer a good didactic tool.

The first edition of this book comprised a selection of syntheses from the five-volume series *The Organic Chemistry of Drug Synthesis* that was in press at that time. Examples were chosen to illustrate the strategy and the organic transformations that were used to prepare the various structural classes that had been investigated as drugs. Research over the decade that has elapsed since the appearance of that first edition saw the birth of many new drugs and perhaps, more importantly, drugs that addressed new therapeutic areas. These also on occasion invoked the use of novel chemistry. These new developments strongly suggested that it was time to bring the book up to date. Many of these new developments are included in this second edition of *Strategies for Organic Drug Synthesis and Design*. This new work is taken from the two volumes of *The Organic Chemistry of Drug Synthesis* that appeared after the publication of the first edition (Volume 6, 1999, Volume 7, 2008).

One of the main motivations that led to the writing of the original book, entitled *The Organic Chemistry of Drug Synthesis*, was curiosity as to how various classes of drugs were in fact prepared. The enormous number of compounds reported in the literature as potential drugs led to an early decision to restrict the book to those agents that had been granted nonproprietary names. This filtering mechanism was based on the assumption that, in the judgment of the sponsor, the compound in question showed sufficient activity to merit eventual clinical evaluation. Within a few years of the publication of *The Organic Chemistry of Drug Synthesis*, a followup volume was issued to bring the coverage up to date and to make up for gaps in the coverage of the original book. Between them, the two books included a large majority of compounds that had been granted generic names up to that time. The subsequent three volumes of what became a series appeared roughly semidecenial in order to cover the syntheses of compounds granted generic names during those intervals. A full decade elapsed before the most recent volume appeared due to a slowdown in the appearance of new compounds granted USAN.

The focus of this book differs from that of the series in that it is aimed more specifically at the organic chemistry used for preparation of the drugs in question. Drugs have been selected mainly for the illustrative value of the chemistry used for their synthesis, and hence, too, the inclusion of the rather extensive "Reaction Index." The structures in chemical schemes have been drawn with special attention to clarifying the individual reactions; rearrangements, starting materials, and products, for example, are shown in similar views. The very brief discussions of medicinal chemistry are intended to provide the reader with a feel for the activities and occasionally the mechanisms of action of various drugs. Salient principles of drug action are presented in capsule form at appropriate points; by the same token, the claimed therapeutic effect of each agent is noted along with the discussion of its preparation. The pharmacological presentations are thus abbreviated over those that occur in the series. Interested readers should consult any of a wide selection of medicinal chemistry or pharmacology texts such as *Burger's Medicinal Chemistry* for fuller and more authoritative discussions.

A word on bibliographic references is in order at this point. The patents that comprise a significant proportion of references were often not readily accessible 10 years ago; to help the reader, those were usually accompanied by a reference to that patent recorded in *Chemical Abstracts*. The ready availability of actual images to U.S. patents (www.uspto.gov) and those from abroad (http://ep.espacenet.com) has led to the deletion of the now-superfluous *Chemical Abstracts* reference.

DANIEL LEDNICER
North Bethesda, MD
March 2008

CONTENTS

CHAPTER 1

PROSTAGLANDINS, PEPTIDOMIMETIC COMPOUNDS, AND RETINOIDS

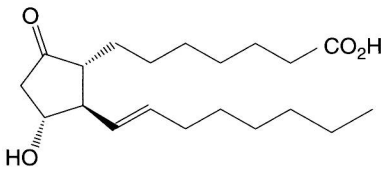
1.1. PROSTAGLANDINS

It is highly likely that those not themselves involved in scientific research perceive the development of new knowledge within a given area of science as a linear process. The popular view is that the understanding of the specific details of any complex system depends on prior knowledge of the system as a whole. This knowledge is in turn believed to derive from the systematic stepwise study of the particular system in question. The piecemeal, almost haphazard, way in which the details of the existence and later the detailed exposition of the arachidonic acid cascade were put together is much more akin to the assembly of a very complex jigsaw puzzle. This particular puzzle includes the added complication of incorporating many pieces that did not in fact fit the picture that was finally revealed; the pieces that would in the end fit were also found at very different times.

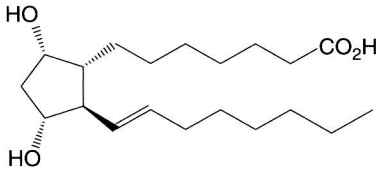
The puzzle had its inception with the independent observation in the early 1930s by Kurzok and Lieb [1] and later von Euler [2] that seminal fluid contained a substance that caused the contraction of isolated guinea pig muscle strips. The latter named this putative compound prostaglandin in the belief that it originated in the prostate gland; the ubiquity of those substances was only uncovered several

Strategies for Organic Drug Synthesis and Design, Second Edition. By Daniel Lednicer

decades later. The discovery remained an isolated oddity until the mid-1960s, by which time methods for chromatographic separation of complex mixtures of polar compounds and spectroscopic methods for structure determination were sufficiently advanced for the characterization of humoral substances that occur at very low levels. The isolation and structural assignment of the first two natural prostaglandins, PGE_1 and PGF_2, were accomplished by Bergstrom and his colleagues at the Karolinska Institute [3]. (The letter that follows PG probably initially referred to the order in which the compounds were isolated: E refers to 9-keto-11-hydroxy compounds and F refers to 9,11-diols; the subscripts refer to the number of double bonds.) The carbon atoms of the hypothetical, fully saturated, but otherwise unsubstituted carbon skeleton, prostanoic acid, are numbered sequentially starting with the carboxylic acid as 1, and then running around the ring and resuming along the other side chain.



PGE_1



$PGF_{1\alpha}$

The identification of these two prostaglandins in combination with their very high potency in isolated muscle preparations suggested that they might be the first of a large class of new hormonal agents. Extensive research in the laboratories of the pharmaceutical industry had successfully developed a large group of new steroid-based drugs from earlier similar leads in that class of hormones; this encouraged the belief that the prostaglandins provided an avenue that would lead to a broad new class of drugs. As in the case of the steroids, exploration of the pharmacology of the prostaglandins was initially constrained by the scarcity of supplies. The low levels at which the compounds were present, as well as their limited stability, forced the pace toward developing synthetic methods for those compounds. The anticipated need for analogues served as an additional incentive for elaborating routes for their synthesis.

Further work on the isolation of related compounds from mammalian sources, which spanned several decades, led to the identification of a large group of structurally related substances. Investigations on their biosynthesis made it evident that all eventually arise from the oxidation of the endogenous substance, arachidonic acid. The individual products induce a variety of very potent biological responses, with inflammation predominating. Arachidonic acid, once freed from lipids by the enzyme phospholipase A_2, can enter one of two branches of the arachidonic acid