STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

Volume 2

Edited by

Thomas Lindberg

Sir Derek Barton

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With a foreword by

Sir Derek Barton
Nobel Laureate in Chemistry

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FOREWORD

The first volume of *Strategies and Tactics in Organic Synthesis*, edited by Thomas Lindberg, was inspired by an article by Dr. I. Ernest, of the Woodward Institute, on the real story behind the late R. B. Woodward's synthesis of prostaglandin. We learned that Nature did not always do what R. B. Woodward told it to do!

Candor in explaining how one really reached one's synthetic target is a virtue not shared by most academic chemists when they publish in learned journals. There are two reasons for this. One is that space restrictions discourage the presentation of negative, or misleading, experiments. The second is that R. B. Woodward, and many others who have followed, chose to publish as if all the steps in a synthesis had been so carefully planned beforehand that the final product was bound to be obtained—provided, of course, that the effort applied was sufficiently diligent and skillful. At the beginning, before the academic community realized that long-planned Woodwardian syntheses were possible, this attitude was stimulating to the advance of organic chemistry. However, now that so many synthetic chemists are able to emulate the early Woodwardian achievements, one must ask the question, Is it worth the effort? It is worth the effort if new principles emerge—like orbital symmetry control, or new reactions such as Eschenmoser's elegant photochemical cyclization in the second synthesis of vitamin B_{12}, or new reagents. But a synthesis, however long and difficult, which uses known principles, known reactions, and known reagents can only contribute to chemistry by accident. This is a costly way to be original. It is much more cost effective to think more and do less.

This second volume of *Strategies and Tactics in Organic Synthesis* continues the same, healthy theme as the first. In showing more frankly

how academic synthetic work is really done, an important service is rendered to all chemists. Our friends in inorganic and physical chemistry can also learn from these articles because the point of view of those outside organic chemistry is that because we pretend that organic synthesis can be planned, it cannot be research anymore and therefore is not worth doing.

An academic chemist who begins a long synthesis soon learns about the importance of a high yield in each step. However, in presenting work later, the yields are not always mentioned and, in particular, the overall yield is not given. It can often be nearly zero. Fortunately, our friends in industry are always conscious of the yield problem. Contact with the real chemical life of industry helps the academic chemist to purge his intellectual system of false pride.

This second volume is as good, or better, than the first. I can strongly recommend it to all who are interested in synthetic chemistry, and especially to those who think that the subject is dull and uninteresting.

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PREFACE

It is indeed a pleasure to be writing the preface to the second volume of *Strategies and Tactics in Organic Synthesis.* The theme of the second volume is the same as that of the first: to give students a "behind-the-scenes" look at organic synthesis from the perspective of outstanding organic chemists.

Students can easily get a mistaken impression of organic synthesis by reading the primary journals—long syntheses of natural products look easy and straightforward. Synthetic dead-ends, blind alleys, and difficulties are rarely mentioned, partly because of space limitations. As both of these volumes illustrate, syntheses rarely turn out the way they were initially planned. In reality, one can plan a reasonable, rational, "paper" synthesis only to go into the lab and discover that the reactions don't want to work the way they should. One then starts changing variables—solvent, temperature, pressure, catalysts—until the reaction is made to work. If the reaction refuses to work, the synthetic route has to be modified. Perseverance is certainly a quality that organic chemists should have.

I owe a special debt of gratitude to the contributors for making this book possible. It is my special pleasure to welcome Amos Smith back for an encore. I hope that readers find the second volume as interesting and informative as the first.

THOMAS LINDBERG

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Chapter 1

DIELS–ALDER REACTIONS OF HETEROCYCLIC AZADIENES: DEVELOPMENT OF A STRATEGY FOR THE TOTAL SYNTHESIS OF STREPTONIGRIN, LAVENDAMYCIN, AND SYNTHETIC QUINOLINE-5,8-QUINONES

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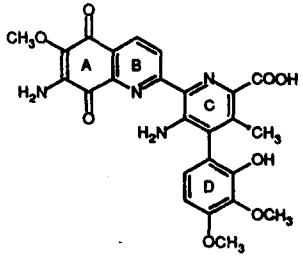
STRATEGIES AND TACTICS
IN ORGANIC SYNTHESIS, VOL. 2

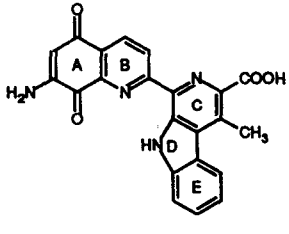
I. Introduction

At the onset of much of our work we have elected to select synthetic targets which possess a significant or contemporary synthetic challenge and which possess biological properties which merit further investigation. At the very least we hope to develop or apply new synthetic methodology that is especially suited for application in the total synthesis of the structure under consideration and, concurrent with these efforts, to design and prepare structurally related compounds which would permit us to address or define the structural characteristics of the naturally occurring material that are responsible for and/or potentiates the observed biological properties. These latter considerations are facilitated if we or others have previously studied or speculated on the agent's *chemical* mechanism of action that is responsible for the observed or expressed biological effects.

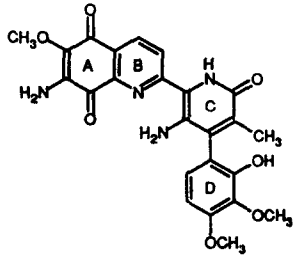
Streptonigrin (**1**),[1] lavendamycin (**2**),[2] and streptonigrone (**3**)[3] are three structurally and biosynthetically related antitumor antibiotics isolated from *Streptomyces flocculus, Streptomyces lavendulae*, and an unidentified *Streptomyces* species (IA-CAS isolate No. 114), respectively. Each possesses a characteristic, highly functionalized 7-aminoquinoline-5,8-quinone AB ring system and a fully substituted pyridyl C ring central to its structure. Consequently, the effective assemblage of the pentasubstituted pyridyl C ring of **1–3** coupled with a divergent approach to the introduction of the streptonigrin/lavendamycin quinoline-5,8-quinone AB ring systems was formulated initially as the key to the total synthesis of members of this class of naturally



1 Streptonigrin



2 Lavendamycin



3 Streptonigrone

occurring antitumor antibiotics. Based largely on the work in progress in our laboratories as well as information available from the extensive investigations of Professors Sauer[4] and Neunhoeffer,[4] our approach to the construction of the pentasubstituted pyridyl component of the naturally occurring materials was expected to be addressed with the implementation of inverse electron demand Diels–Alder reactions of electron-deficient heterocyclic azadienes.

Streptonigrin was first identified and characterized in 1959,[1a] its structure was correctly determined in 1963[1b] using a combination of classical chemical degradative studies coupled with the application of the then emerging spectroscopic techniques of infrared, ^{1}H NMR, and mass spectrometry, and subsequently was confirmed in 1975 with a single-crystal X-ray structure determination.[1c] Since the initial structure determination, streptonigrin has been the subject of extensive synthetic, biosynthetic, and biological investigations which have resulted from a continued interest in its confirmed antimicrobial, cytotoxic, and antitumor properties.[5] In no small part, the synthetic challenges posed by the streptonigrin structure, which include its concentrated array of reactive functionality and the presence of stable CD biaryl atropisomers,[1e] investigations on the chemical mechanism by which streptonigrin expresses its biological effects,[4,6] efforts to define the essential structural features required for observation of this activity,[4–7] and revealing biosynthetic investigations account for the continued interest in this structure.[4,8] Information and work derived from the completed total syntheses[9,10] of streptonigrin [Weinreb *et al.* (1980) and Kende *et al.* (1981); cited in Chart I] and from the extensive preliminary investigations[4,11,12] of Cheng, Rao, Lown, Kametani, Martin,[13] Kende, Weinreb, and Cushman contributed substantially in the planning and execution of our own efforts.[14]

The structure identification of lavendamycin (**2**), which was disclosed in 1981,[2] rested exclusively on extensive spectroscopic studies on a limited supply of naturally occurring material which were guided by biosynthetic considerations. It is a tribute to the advances in modern spectroscopic techniques that lavendamycin was initially and correctly identified with the available naturally occurring material using principally ^{1}H/^{13}C NMR information, ultraviolet and infrared spectroscopy, and high-resolution mass spectral exact mass determinations, guided correctly by prior biosynthetic postulates for intermediates potentially involved in the biosynthesis of streptonigrin.[8,15] Thus, in contrast to the earlier structure elucidation of streptonigrin (**1**), classical chemical degradative studies played little apparent role in the structure identification of lavendamycin. Unambiguous confirmation of the proposed lavendamycin structure was accomplished by subsequent total syntheses.[16,17] Most notably, Kende's approach to lavendamycin, which has been concurrently pursued by the Hibino and Rao

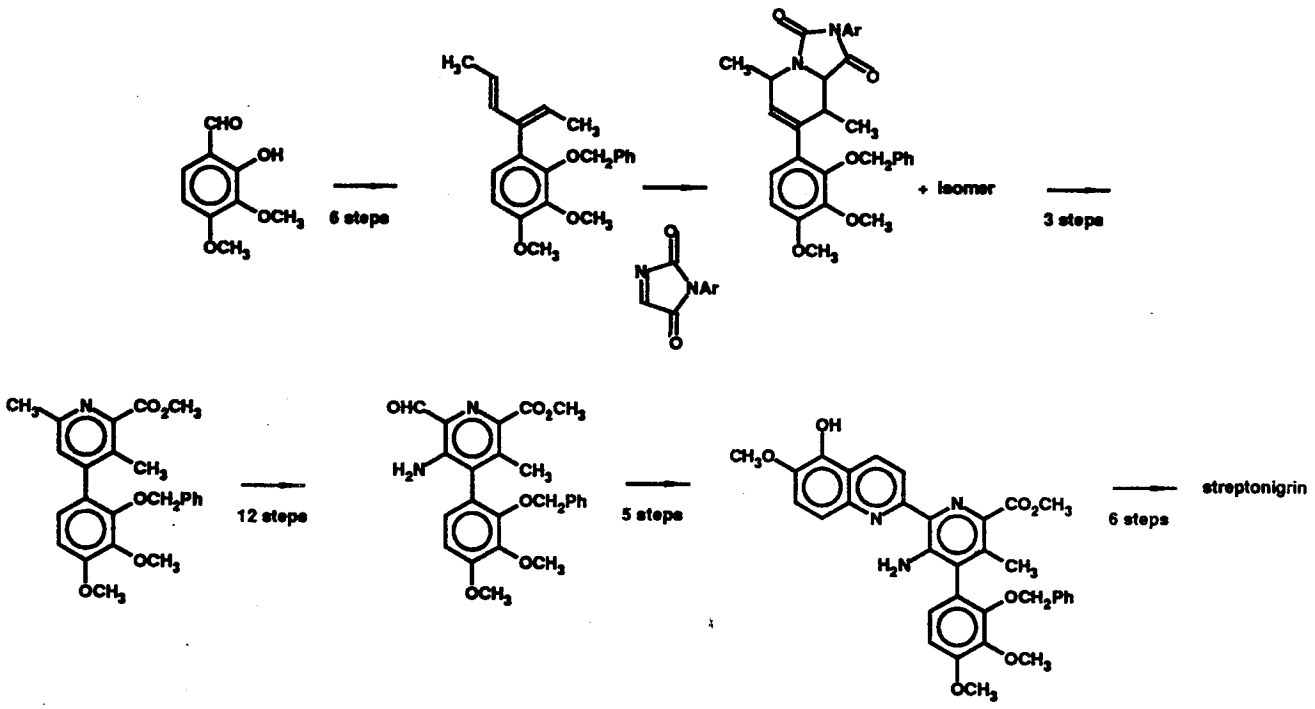


CHART 1. Summary of streptonigrin total syntheses. Top, Ref. 9; Bottom, Ref. 10.