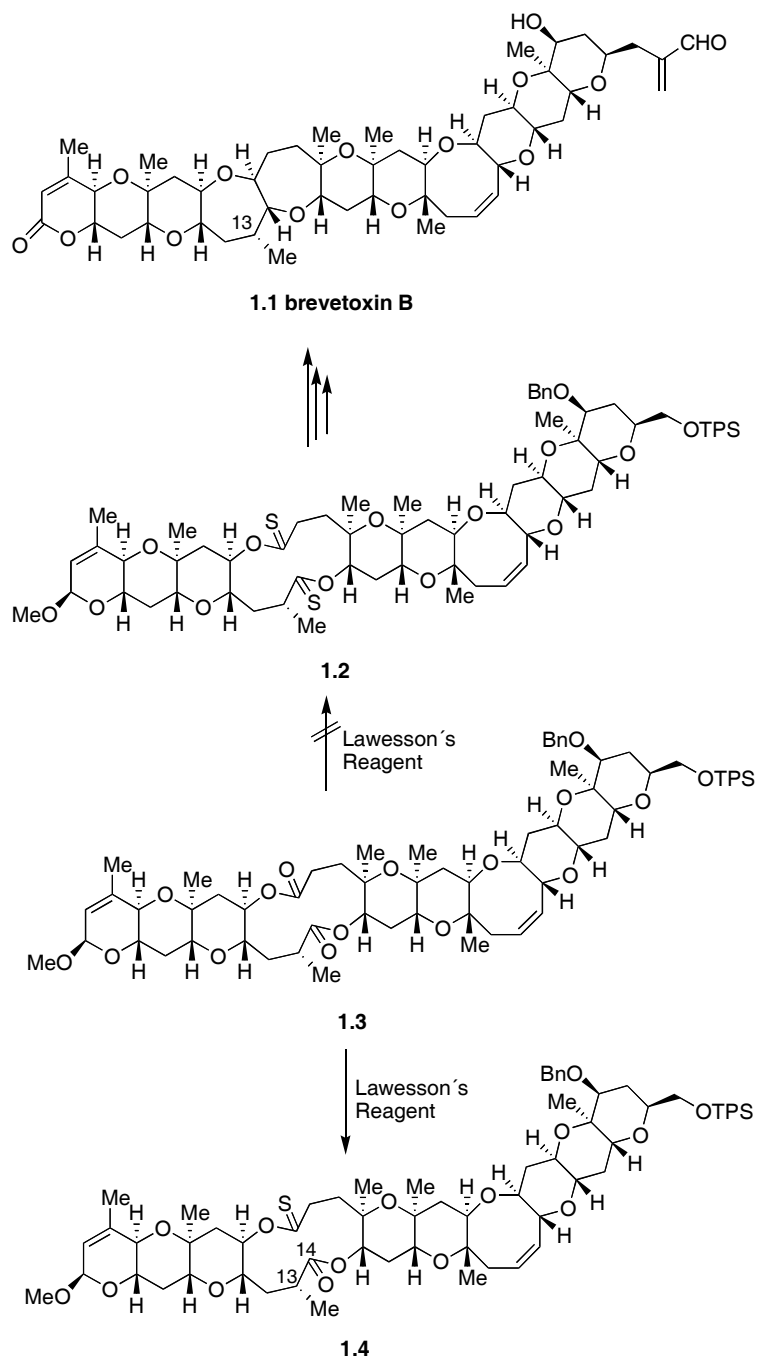


Chapter 1

Introduction: From the Paper to the Laboratory

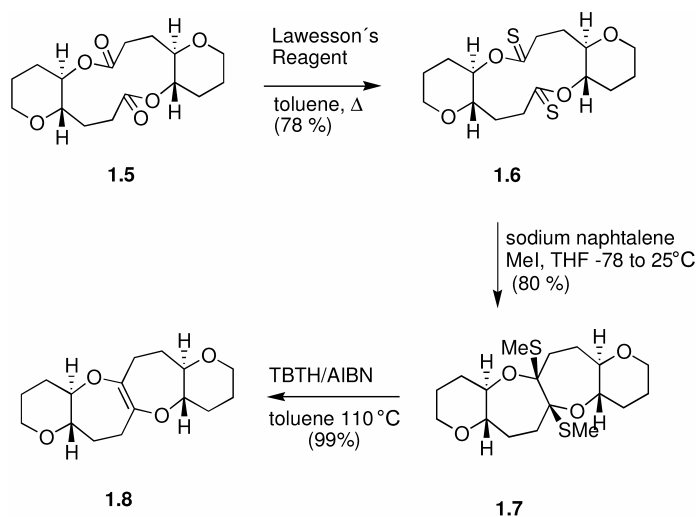
Seven years ago we began to write a long article for *Angewandte Chemie International Edition* [1] pointing to an aspect of modern organic synthesis that, in our opinion, had been neglected: the difficulties in reaching a synthetic target. The introduction of that article said *much of the current chemical literature deals with the synthesis of organic molecules or describes the development of methodology for organic synthesis. The achievements of synthetic methodology are impressive and the most complex molecules are, in principle, accessible. From the beginning of the 90's a feeling has been spread throughout the chemical community about the maturity of this branch of chemistry, and today terms such as atom economy, highly efficient homogeneous and heterogeneous catalytic transformations, combinatorial chemistry, and so on, are frequently used when talking about organic synthesis.*

Great optimism arises from the chemical literature when describing how the molecules are synthesized. It seems that our ability to devise synthetic routes has become infallible, and that even the most complex target molecules are prepared without apparent effort. Is this always true? or is a lot of effort still necessary to make every step in a multi-step synthesis possible? The readers of papers that describe the preparation of organic molecules are very familiar with sentences such as "after extensive experimentation it was found, to our delight, the reaction worked nicely", and other examples thereof. Apparently, to go into detail about the failures or to discuss all the unfruitful approaches, decreases the beauty of the synthetic route reported. Therefore, it is not often easy to recognize when the synthesis has developed as planned. In the meantime a lot of useful information may be lost. The aim of this work is to look at the total synthesis from a different point of view. We will focus on the detours from the original synthetic plan, the dead-ends that may arise at specific steps of a total synthesis, as well as the thinking involved in solving the problems en route to the synthetic goal. Often, the final route is at least of equal beauty to that originally planned. The selection of problems discussed below has been extracted from papers that explicitly expressed the failure of the original plan, and the evolution to the final successful (or in some cases unsuccessful) solution of the problem.



Nicolaou's brevetoxin B synthesis [2] was used as the first example to show how the failure of a well-tested transformation can truncate a total synthesis in an advanced step. The transannular bridging of the 12-membered bis-(thiolactone) **1.2** was designed to build the remaining two rings of brevetoxin B **1.1** (Scheme 1.1).

The process had been thoroughly tested in model systems like **1.6** [3] (Scheme 1.2) and seemed to be a very attractive strategy to prepare the desired final product. However, all the attempts to prepare compound **1.2** by reaction of the macrodilactone precursor **1.3** with Lawesson's reagent produced very low yields of the desired bis(thiolactone) **1.2**. The lactone carbonyl at C14 remained unaltered, and the reaction product was monothiolactone **1.4**. Other Lawesson-like reagents were also unable to form **1.2**, and this route was eventually abandoned. In spite of this apparent failure, a full body of methodology to build fused seven-membered rings was developed in the process. The successful synthesis of brevetoxin B by Nicolaou and co-workers is now a landmark in organic synthesis [4].



Scheme 1.2

We have searched the literature to find another example that better illustrates the ideas to be discussed in this book but have failed. This example exceptionally shows how the failure of a single transformation can thwart a beautiful idea making the planned synthesis unfeasible. However, the advantage is the acquisition of an exceptional amount of knowledge, which is, in the end, the object of chemical synthesis.

During the long process of publishing our review, interesting discussions with the reviewers demonstrated that our opinions about how to present total organic synthesis were not generally shared by the scientific community. We are going to include two of these points of view; the first one was written by one anonymous referee and stated:

“failed” reactions often lead to results which are not clean. These are usually described in papers as giving “decomposition of starting materials” or complex mixtures of products”. For those involved in Organic Synthesis such reactions seem to occur far too often! From such experiments conclusive and/or publishable information is difficult to glean. Reporting of results in this fashion, while being honest, does not provide much information from which the reader can learn and is often avoided. Second: often Organic Synthesis relies on luck! It doesn’t matter how well planned a synthesis is, the route is nearly always going to have stages which are risky and predictably so, in advance. Such risks are assessed in the planning stages before undertaking synthetic work. It may sometimes be judged that a very high-risk strategy may offer significant potential benefits, which warrant investigation. Failures of high-risk work may go unreported as with the benefit of hindsight they may look to have strayed across the border between courageous and foolish!

The second different point of view against reporting excessive details about failures was written by Danishefsky: *Before relating a few of these episodes (referring to the synthesis of some of the many molecules synthesized in his group), some important cautionary notes and attributions are in order. For those schooled in the art (of Organic Synthesis), there will be little need for either. The experienced practitioner is well aware that the pathways of synthesis are circuitous, bumpy, and even treacherous. Seldom do straight lines suffice to connect points in a synthesis of real consequence. Hence, the seasoned chemist will appreciate that along with these “magic moments” of success, one could have reported a litany of setbacks and reversals. However, for younger and more optimistic enthusiasts, it is appropriate to underscore the uncertainties, the detours and, yes, the frustrations associated with Organic Synthesis. Success is often a prize reserved for those who temper noble ideas with appropriate measures of realism and skepticism. Given the episodic nature of our science, wisdom may well be more valuable than cleverness. The ability to plumb the implications of each experiment, positive and negative, is central to the process of learning as we go along. Our quest to reach the promised land should not render us insensitive to opportunities for discovery, even as we find our way through the desert [5].*

We are going to try, through this book, to show how the difficulties encountered in a total synthesis, lead to an increase in knowledge. Much has been learnt during the seven years after we commenced the work from which this book is derived. We still believe that the difficulties encountered, while implementing many synthetic routes in the laboratory, are not due to any intrinsic unpredictability of this science. This is an idea that may arise from this book, but is far from reality. We are going to discuss superb synthetic achievements and the idea is not unpredictability but necessity for knowledge. Organic synthesis is still very far from becoming a closed science. The words written by Corey [6]: *In many respects, the development of the synthesis of okaramine N was similar to finding a way up a vertical cliff that offers just a limited number of small cracks and handholds*, clearly demonstrate our necessity for knowledge to increase the number of cracks and handholds available to climb any vertical cliff, present or future.

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