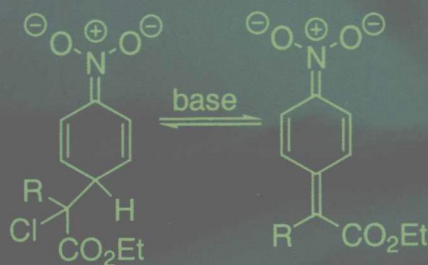


M. Gómez Gallego

M. A. Sierra

Organic Reaction Mechanisms

40 Solved Cases



Springer

Mar Gómez Gallego • Miguel A. Sierra

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40 Solved Cases

With 432 figures, 116 in colour



Springer

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Organic Reaction Mechanisms

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Foreword

Teaching organic chemistry is a difficult task. One reason is the large gap between the observable properties of a given chemical species and its formal representation on a blackboard or on a computer screen. This concern is even more important in the case of the elucidation of reaction mechanisms, since it involves entities such as reaction intermediates or transition states which are difficult, if not impossible, to observe. The second (obvious) reason is that organic chemistry is an experimental science. We do not have in our discipline any “theorem of stereocontrol” for example, although we have experimental data and mechanistic models that provide us with conceptual tools to explain or even to predict the stereocontrol of a new experiment in organic chemistry. Therefore, according to Popper, we cannot demonstrate that a given mechanism is “true” although we can conclude that it is “false” if it is not compatible with the experimental observations. In addition, the concept of reaction mechanism can be misleading because in many textbooks it is implicitly assumed that there is a common mechanism for, let us say the Diels Alder-reaction although we know that any cycloaddition can be stepwise or concerted.

This book constitutes an innovative contribution within this context. The authors have collected very illustrative problems that cover the main topics of organic chemistry. However, they have not followed the usual admonitory way in which only the correct answers are commented. Instead, the authors show the possible alternative mechanisms and how the experimental data provided by carefully designed experiments can help to discard very plausible hypotheses.

In summary, the reader, after studying the problems presented and discussed in this book, will appreciate not only the beauty and diversity of organic chemistry, but also the necessity of being creative and (reasonably) unbiased as well as sceptical and cautious when confronted with novel mechanistic problems.

University of the Basque Country, June 2003

Fernando P. Cossío

Preface

These are the times of highly sophisticated computer programs that lead to pretty pictures about how an organic reaction works. Nevertheless, the knowledge of the mechanism of an organic reaction is still derived from very hard experimental work and the ability to process and to get information from the data obtained. The interpretation of the experimental data is a key point in the formation of organic chemists, independent of their future work. It is sometimes confusing to learn how to do this in a jumble of equations, theoretical studies, and physical-chemistry postulates. The approach we have chosen for this work is a practical one. Instead of formulating study mechanisms from the diverse theories and experimental methods in the classical way, the aim of this book is to discuss a series of selected examples of organic reaction mechanisms to understand how they have been proposed.

All the cases presented have been taken from recent literature and deal with the formulation and experimental determination of a mechanistic proposal. They are based on real cases that demonstrate how nowadays organic chemists are still deeply concerned about insights into a reaction. Through the book we use any type of information that the authors of the original work considered necessary in the elucidation of the reaction mechanism. This includes spectroscopic data, kinetic and thermodynamic data, isotopic labelling, theoretical studies ... and of course, the knowledge of the reactivity of organic compounds.

The examples have been ordered into three levels. Level 1 is dedicated to revising fundamental concepts regarding the elucidation of an organic reaction mechanism. The subjects discussed in this level will be the tools to be used later in levels 2 and 3. Level 1 starts with the most immediate source of information when studying an organic reaction mechanism, the structure and stereochemistry of the reaction products. Basic concepts regarding crossover experiments, neighboring group participation and classical/nonclassical carbocations are followed by some examples that illustrate the use of isotopic labelling in mechanistic studies. The importance of data obtained from kinetic measurements is discussed later and subjects like catalysis in solution, Hammett constants, activation parameters and kinetic isotope effects are revised. To complete this first part of the book, there are some examples dedicated to revising the different types of pericyclic reactions such as cycloadditions, electrocyclic ring closures and sigmatropic rearrangements.

Once the fundamental concepts have been established, they are all combined in the discussion of the collection of examples proposed in levels 2 and 3. Now the cases have been placed in order of increasing difficulty from easy to medium in level 2 and medium to difficult in level 3, mixing the different techniques and data to understand the different aspects of the example under discussion. All examples are treated in detail following the same methodology: introduction, experimental data and discussion. Key points, additional references and solved questions related to the main subject studied are also included.

This book is aimed to advanced undergraduates in chemistry but it also may be useful for the instructors who should be able to find in the text new examples to illustrate topics of advanced organic chemistry or physical organic chemistry. A good knowledge of organic chemistry, how to write an organic reaction mechanism, and a basic understanding of the basics of physical organic chemistry is presumed for the readers in order to get the most out of each case. The work done by the authors of the papers used to build up this book has made possible the discussion of mechanistic concepts from an organic chemistry basis. Moreover, their work demonstrates that experimental mechanistic studies are still alive and are necessary to understand the insights of an organic process.

June 2003

Mar Gómez Gallego
Miguel A. Sierra

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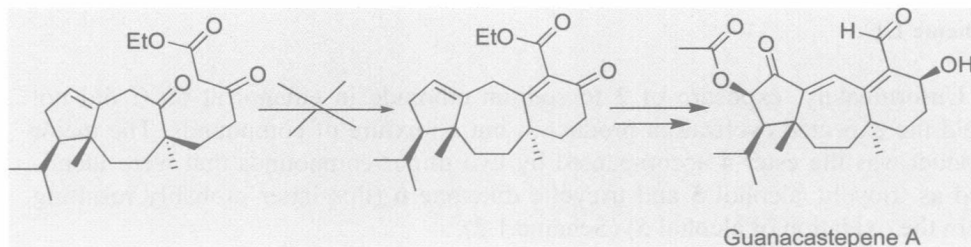
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Level 1 – Case 1

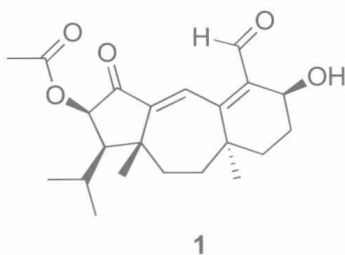
A Surprise in the Synthesis of Guanacastepene A

Key point: *Unexpected result in a well-known reaction*

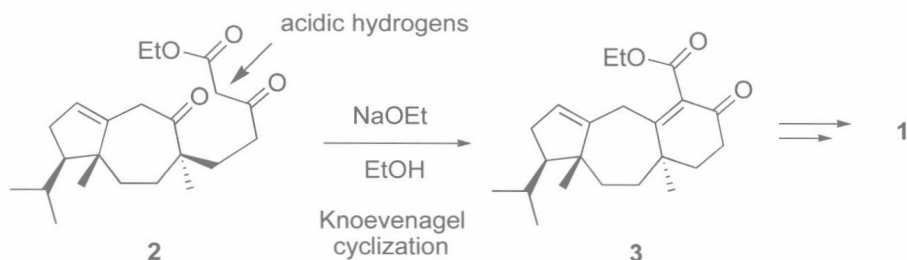


A Surprise in the Synthesis of Guanacastepene A

Sometimes a reaction with a well-established mechanism does not work as expected. In these cases the mechanism has to be reinvestigated and the careful analysis of the reaction products usually gives the key of the mechanistic pathway. This situation can be found in multistep synthetic sequences that have been designed to achieve a target molecule and that are based on the *predictable* outcome of each step. We have an example in the synthesis of guanacastepene A **1**, the parent member of a family of diterpene natural products obtained from a fungus. This compound is a synthetic target of current interest due to its novel structure and the possibility of exploring its activity against antibiotic-resistant bacteria.

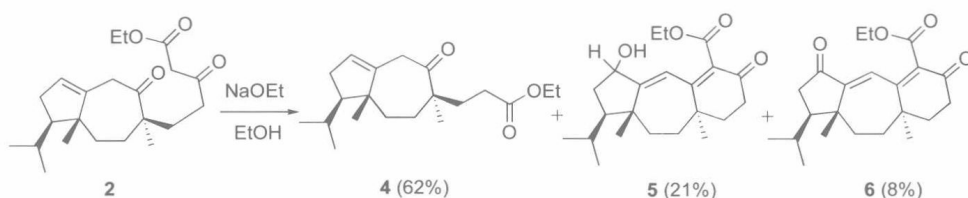


One of the diverse approaches to the synthesis of **1** is based on the formation of the tricyclic core of guanacastepene **3** by means of a direct Knoevenagel cyclization of β -keto ester precursor **2** (Scheme 1.1).



Scheme 1.1

Unfortunately, exposure of **2** to sodium ethoxide in ethanol at 60°C did not yield the expected cyclization product **3**, but a mixture of compounds. The major product was the ester **4** accompanied by two minor compounds that were identified as tricyclic alcohol **5** and tricyclic diketone **6** (this latter probably resulting from the oxidation of alcohol **5**) (Scheme 1.2).¹



Scheme 1.2

*Suggest a reasonable explanation for the failure of the Knoevenagel cyclization of compound **2**. Propose a mechanism to justify how compounds **4** and **5** are obtained. To answer these questions use the information attained in the following experiments.*

Experimental Data

Exposure of the dioxolane-protected β-keto ester **7** to the Knoevenagel cyclization conditions did not result in the formation of the ester **8** (Scheme 1.3).

¹ The configuration of the alcohol in **5** was tentatively assigned as shown in Figure 1.1 upon NOESY experiments.

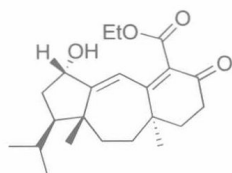
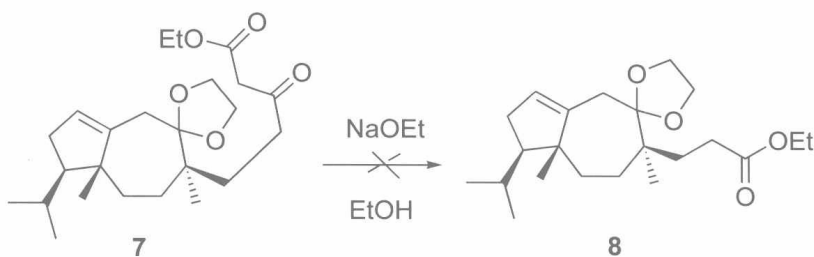
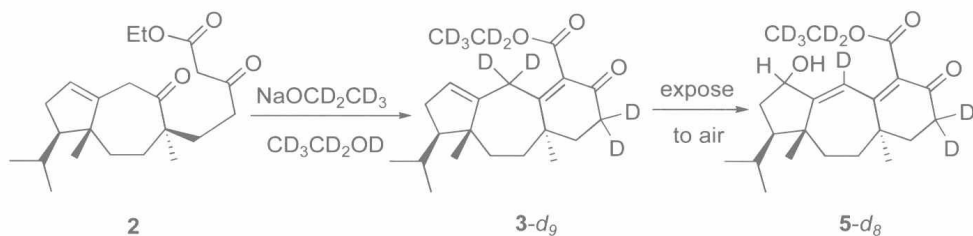


Figure 1.1



Scheme 1.3

The cyclization of **2** was carried out in deuterated solvent and base. When the reaction was performed with rigorous exclusion of air, the expected Knoevenagel product, deuterated in nine positions (**3-d₉**) could be detected by mass spectrometric analysis of the crude reaction mixture. Furthermore, octadeuterated tricyclic alcohol (**5-d₈**) was obtained as the only reaction product after the reaction mixture was exposed to air (Scheme 1.4).²



Scheme 1.4

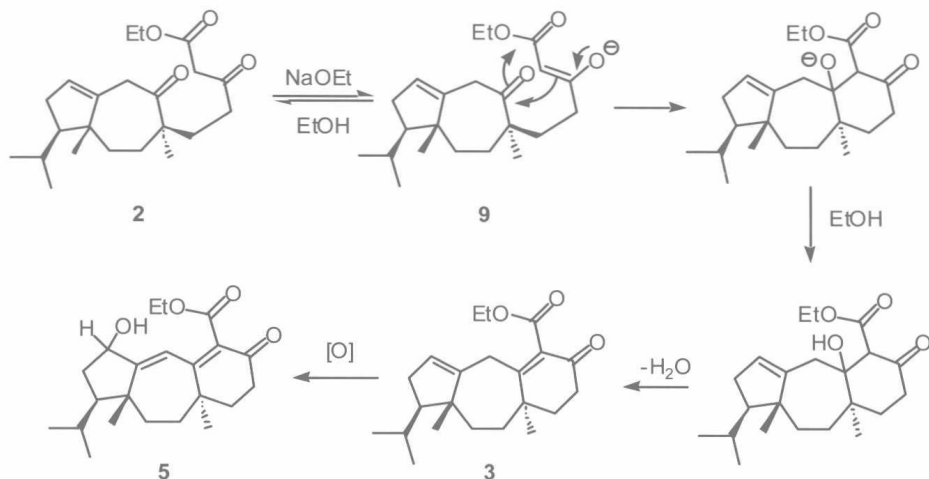
Discussion

◀The starting point in the investigation of a reaction mechanism is always the analysis of the number of products obtained in the reaction and the determination of their structures.▶ Particularly, from the study of the structure of the reaction products we can obtain valuable information about the bonds that have been broken and those that have been formed during the process. In this case, the analysis of the structure of the reaction products **4** and **5** is the key to understanding why an ideal substrate for a Knoevenagel condensation as β -keto ester **2** reacts in a different way.

Considering the structures of the reaction products **4** and **5** we notice that tricyclic alcohol **5** resembles the expected Knoevenagel product (although it has been oxidized), but in the case of **4** the structure is completely different. It is very unlikely that two products, so different from each other, would come from a single reaction pathway. Hence, a much more reasonable option is to consider *two competing reaction pathways* when **2** was treated under Knoevenagel conditions.

² Compound **5-d₈** was identified by ¹H NMR. The methine (CHOH) proton ($\delta = 4.38$ ppm) appeared only after the reaction mixture was exposed to air.

Let us start with alcohol **5**. The results obtained in the deuteration experiment confirm that **5** was obtained by oxidation of the expected Knoevenagel product **3**. Thus, β -keto ester enolate **9** is already formed in the reaction medium and does in fact lead to the desired unconjugated tricycle **3**, although this compound undergoes rapid oxidation and cannot be isolated (Scheme 1.5). Evidently, further oxidation of the alcohol **5** leads to the tricyclic ketone **6**, which is also detected in the reaction mixture.

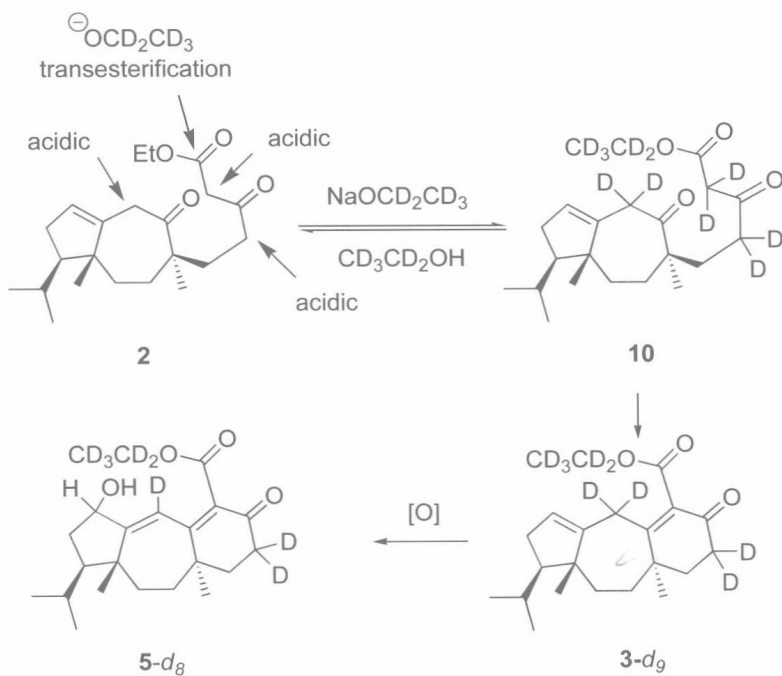


Scheme 1.5

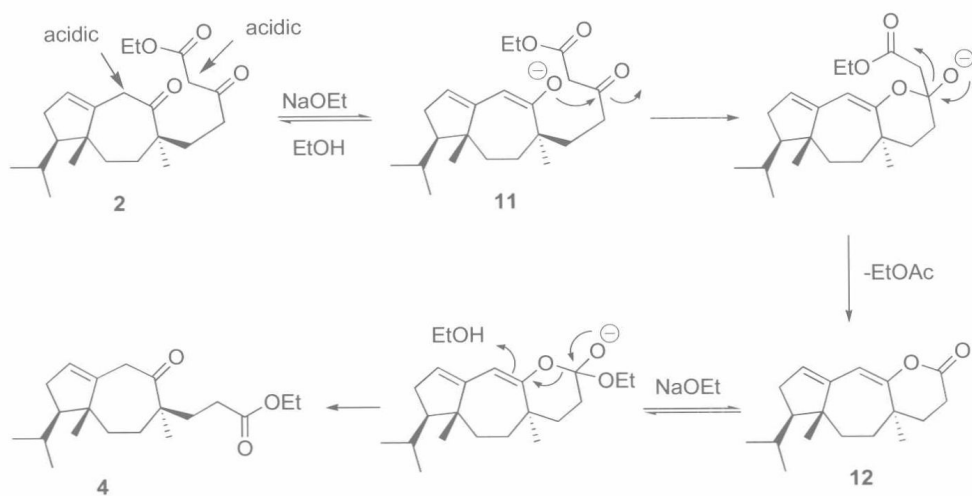
Does this mechanism agree with the position of the deuterium labels in **5** when the reaction was carried out in deuterated base and solvent? The starting compound **2** has several acidic positions (α to the ester and α to the keto groups) that can exchange protons with the solvent. In addition, in the presence of deuterated ethoxide, transesterification of the carboxylate group can also occur. The starting material in the deuterated medium will be **10** rather than **2**. Following the Knoevenagel mechanism previously discussed, but now starting from **10**, compounds **3-*d*₉** and **5-*d*₈** are obtained (Scheme 1.6).

Competing with this route is the pathway leading to the major reaction product **4**. To understand how this compound is formed we should have in mind the failure of the reaction when the endocyclic keto group is protected as dioxolane (see Scheme 1.3). This data indicates that a free keto group is essential for the outcome of the reaction.

Compound **2** is distinguished from the typical Knoevenagel cyclization substrates by the enhanced acidity of the unconjugated enone α -protons. Thus, a reasonable alternative to the Knoevenagel mechanism could be to consider that under the reaction conditions, the formation of hydroazulenone enolate **11** would take place. Addition of the enolate oxygen to the keto group should form lactone **12**, which would yield bicyclic ester **4** by addition of the ethoxide to the lactone carbonyl group and subsequent lactone breakage (Scheme 1.7). As the endocyclic keto group in **2** is directly involved in the reaction, dioxolane **7** (which lacks the feature of a participating cyclic enolate) does not undergo this reaction.



Scheme 1.6



Scheme 1.7

In Summary

Although β -keto ester **2** seems to be an ideal substrate for a Knoevenagel cyclization, the expected product is not isolated when **2** is exposed to sodium ethoxide in ethanol. Instead, products derived from two competitive pathways are observed. The major product, bicyclic ester **4** is derived from a condensation involving the cyclic enolate **11** and the minor product, tricyclic alcohol **5** comes from the oxidation of the already formed Knoevenagel product, which cannot be isolated.

Additional Comments

For other interesting surprises in the synthesis of guanacastepene A see Lin S, Dudley GB, Tan DS, Danishefsky SJ (2002) *Angew. Chem. Int. Ed.* 41:2188-2191.

This problem is based on the work by Tan DS, Dudley GB, Danishefsky SJ (2002) *Angew. Chem. Int. Ed.* 41:2185-2188.

Subjects of Revision

Knoevenagel and Claisen reactions.

Level 1– Case 2

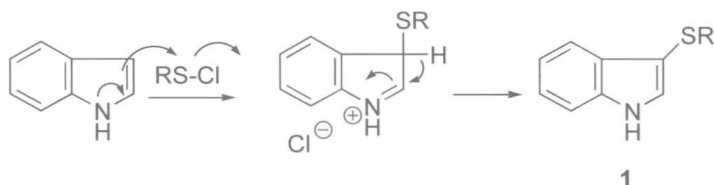
Sulfenylation of Indole

Key point: Structure of products and mechanism



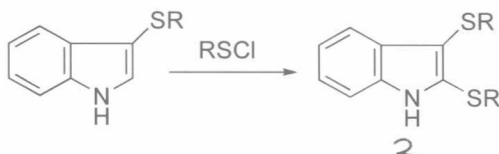
Sulfenylation of Indole

3-Indolyl sulfides **1** are easily prepared by sulfenylation of indoles with sulfonyl chlorides. The mechanism of the sulfenylation is well known and follows the usual S_EAr -type substitution pathway depicted in Scheme 2.1.



Scheme 2.1

One drawback to the use of sulfonyl chlorides for the sulfenylation of indoles is their exceptional reactivity. If the 2-position of the indole is unoccupied, the slightest excess of reagent leads to a second sulfenylation, and a full second equivalent leads to excellent yields of 2,3-indolyl bis-sulfides **2** (Scheme 2.2).



Scheme 2.2

The question to be resolved is the following: *is the second sulfide group introduced directly at the 2-position of the indole ring or is it necessary to consider an alternative mechanism for the formation of bis-sulfides 2?*