# The Dienone–Phenol Rearrangement of Santonin: A Comprehensive Laboratory Experiment for Advanced Undergraduate Organic Chemistry Students

**María I. Colombo, Sebastián A. Testero, Silvina C. Pellegrinet, María L. Bohn and Edmundo A. Rúveda***

*Instituto de Química Orgánica y de Síntesis (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Casilla de Correo 991, 2000 Rosario, Argentina, eruveda@fbioyf.unr.edu.ar*

*Received March 28, 2001. Accepted July 17, 2001*

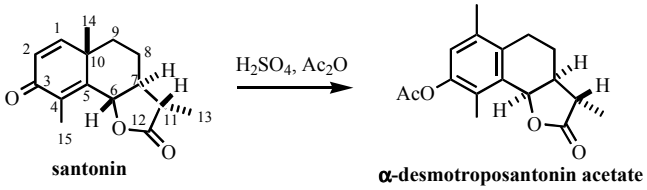
**Abstract:** A comprehensive laboratory experiment suitable for advanced undergraduate organic chemistry students has been designed. The experiment is based on the dienone–phenol rearrangement reaction of the sesquiterpene santonin to give α-desmotroposantonin acetate. It challenges students to solve an earlier controversial stereochemical problem. The students carry out the reaction and analyze spectroscopic data to determine the stereochemistry of the starting material and the product. In addition, they perform simple molecular modeling calculations, which enable them to rationalize the stereochemical outcome of the transformation and discuss the mechanism of the dienone–phenol rearrangement and related rearrangements reported in the literature.

## Introduction

The elucidation of the structure of natural products, in particular those isolated from plants, was one of the most popular research areas of organic chemistry during the first half of the 20th century. There are many examples in the literature that show how difficult it was to determine the structure of relatively complex biologically active compounds such as alkaloids, terpenes, steroids, vitamins, etc. by chemical degradation. This activity stimulated notable progress in organic chemistry because it required an up-to-date knowledge of functional group reactivity as well as a logical understanding of chemical behavior. The birth of physical methods, however, revolutionized the practice of natural product chemistry, particularly in the elucidation of their structures. Today, a not very complicated structure can be solved quite easily using powerful NMR and X-ray diffraction techniques. It is interesting to point out that this turn in the area of natural product chemistry was also reflected in the way of teaching organic chemistry. Most topics from the chemistry of natural products were eliminated from the curricula of organic chemistry courses. Although deleting the analysis of degradative evidence for structural determination is justified by the availability of the effective spectroscopic methods, this change has produced some disadvantages. The chemical logic in structure determination by degradative reactions, the variation of reactivity with structure, participation by neighboring groups, and the notion that many mechanistically important reactions were originated from natural product chemistry are some topics, among others, that were deleted. We think these topics are important enough to be reintroduced in advanced undergraduate courses in some other way [1]. Dostál's recent publication is an excellent example of this [2].

## Results and Discussion

In order to design an instructional experiment that allows this reintroduction, we have chosen the dienone–phenol rearrangement of santonin into α-desmotroposantonin acetate (Scheme 1), as a representative example. We have selected an example that played a crucial role in the studies elucidating the structure of the anthelmintic sesquiterpene santonin [3], including the determination of the controversial configuration at C-11 of this natural product [4]. This transformation was also used to study the synthesis of estrogens by aromatization of ring A of alicyclic steroids. These studies, in turn, gave rise to a passionate debate about the mechanism of the dienone–phenol rearrangement [5].




**Scheme 1**

We use this experiment in our advanced undergraduate organic chemistry course aimed at majors in chemistry, and we have found it more convenient that two students work together. In the first part of the laboratory, students transform santonin [6] into α-desmotroposantonin acetate. The reaction is run at room temperature, can be effectively monitored by TLC, and the yield is excellent. Furthermore, the product is a solid that can be recrystallized for identification.

While the reaction is in progress, the students analyze the spectral data (IR, $^1$H NMR and $^{13}$C NMR) [7] of santonin, which are provided to them together with the structure and absolute configuration of all stereogenic centers present in the

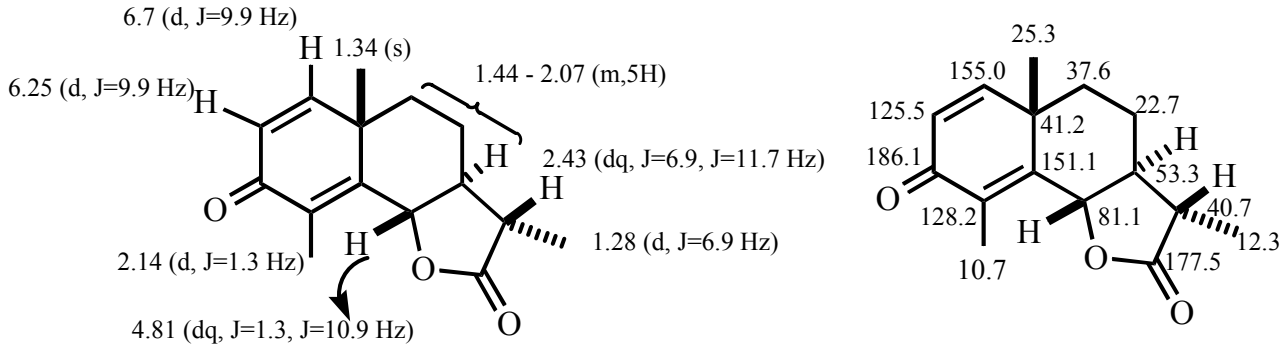



**Figure 1.** IR $\nu_{max}$ ($cm^{-1}$) 1786 (*trans*-lactone), 1654 enone.

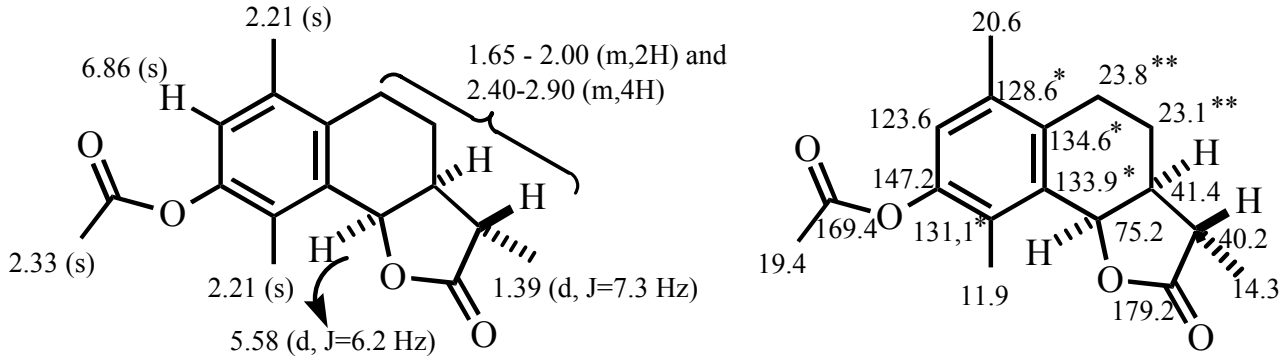



**Figure 2.** IR $\nu_{max}$ ($cm^{-1}$) 1764 (*cis*-lactone and ester).

molecule, except the one at C-11 (Figure 1). Based on this analysis and on the fact that santonin is the more stable epimer, the students should be able to assign the stereochemistry at this stereogenic center and to suggest experiments to confirm this assignment.

The analysis of the coupling pattern of the C-11 methine proton is crucial for the determination of the configuration of this stereocenter. Because the stereochemistry at C-7 is provided to the students, they can deduce, on the basis of the 11.7-Hz value for the coupling constant between the C-7 and C-11 methine protons, their *trans* relationship. It is also important to point out that a coupling constant of 10.9 Hz observed at C-6 methine proton is in agreement with a *trans*-fused arrangement of the lactone ring.

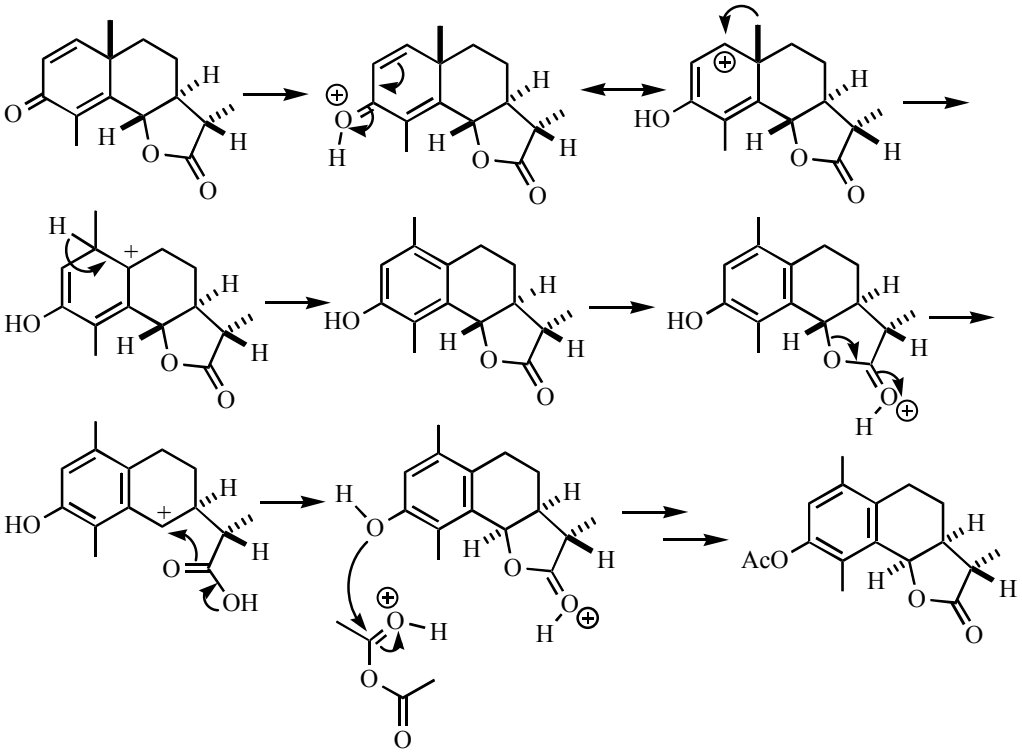
At this stage the students are induced to determine the $\Delta H_f$ values of α- and β-santonin, the two epimers at C-11. The teaching assistants show the students how to use the semiempirical AM1 algorithm from the MacSpartan Plus package (Wavefunction, Inc., Irvine, Calif.) for minimizing the energy of both epimers. The comparison of the computed $\Delta H_f$ values allows the students to confirm the assignment of the configuration at C-11 suggested by $^1$H NMR. Furthermore, the greater stability of α-santonin can be rationalized in terms of the steric interaction experienced by the methyl group at C-11 and the C-8 methylene in β-santonin. This rationalization can be also confirmed by comparing the calculated dihedral angles between C-8, C-7, C-11 and C-13 and their corresponding $^{13}$C NMR shifts in both epimers [8].

Once the reaction is completed the students recrystallize the product, and a sample is submitted for IR, $^1$H and $^{13}$C NMR spectra [7] (Figure 2). Although it would be desirable that the students acquire their own spectra, we have no IR and NMR facilities in our undergraduate students laboratory.

In order to determine the outcome of the reaction, the students are asked to examine major similarities and differences in the IR and NMR spectra of the starting material and the product. The IR spectrum of the product shows that the characteristic stretching frequency of the α-enone has disappeared and that a singlet has appeared in the aromatic region of the $^1$H NMR spectrum. The doublet corresponding to the C-6 methine now has a coupling constant of 6.2 Hz, in agreement with the presence of a *cis*-fused lactone moiety. Unfortunately, the overlapping of the signals corresponding to the C-7 and C-11 methines with the complex multiplets corresponding to C-8 and C-9 methylenes, prevents the analysis of the coupling constants between both methines. However, the comparison of the $^{13}$C NMR shift of the C-11 methyl group signal of α-desmotroposantonin acetate with the reported value for the same carbon of β-desmotroposantonin acetate [8], shows that the stereochemistry at C-11 has had no change in the transformation (Figure 2).

Again, the inversion of configuration at C-6 observed in this reaction is supported by the comparison of the computed $\Delta H_f$ values of α-desmotroposantonin acetate and 6-epi-α-desmotroposantonin acetate. This comparison shows that the thermodynamically favored product is in fact formed in the reaction.

The students are then encouraged to propose a mechanism for this dienone–phenol rearrangement based on the experimental and computed evidences obtained by themselves, in order to compare with related rearrangements from the literature [5].



**Scheme 2**

The acid-induced rearrangements of several bicyclic cyclohexadienones were analyzed under a variety of reaction conditions, and several mechanisms were proposed to explain their behavior [9]. Based on those results and on kinetics studies on α-santonin itself [10], it was suggested that under strong acidic conditions the mechanism of the transformation of α-santonin into α-desmotroposantonin acetate involves a fast protonation of the dienone's carbonyl group followed by the rate-determining rearrangement to give the intermediate 6-epi-α-desmotroposantonin. The subsequent ring opening and reclosure of this intermediate *trans*-lactone, through a benzylic carbocation, leads to the thermodynamically favored *cis*-fused lactone, which, upon acetylation, gives α–desmotroposantonin acetate (Scheme 2).

## Conclusions

The assignment of the configuration, which was at one time controversial, at C-11 of santonin and the structure and stereochemical elucidation of the *cis*-lactone ring present in α-desmotroposantonin acetate [4] by using spectroscopic and computational data obtained by the students and the discussion of the mechanism of this dienone–phenol rearrangement, together with some of those historically important ones interestingly described by Berson [5], are the most important features of this experiment. The goal of this final discussion is to give the students an idea of the difficulties found by outstanding chemists of the 20th century in trying to obtain the structural guiding principle and reaction conditions of dienone–phenol rearrangements and, as a consequence, of how organic chemistry has developed.

**Acknowledgment.** We thank Dr Brian Coppola for his critical review and suggestions to improve this manuscript, Dr Manuel González Sierra for the NMR spectra determinations and helpful discussions and the anonymous referee for very useful, in-depth comments. Financial support from UNR, Fundación Josefina Prats, CONICET and Agencia Nacional de Promoción Científica y Tecnológica is gratefully acknowledged.

**Supporting Material.** A copy of the students' lab assignment is available at http://dx.doi.org/10.1007/s00897000511b.

## References and Notes

1. Hanson, J. R. *Educ. Chem.* **1998,** *35,* 28.
2. Dostál, J. *J. Chem. Educ.* **2000,** *77,* 993–998.
3. Simonsen, J.; Barton, D. H. R. *The Terpenes,* Vol. III; Cambridge University Press: New York, 1952, pp 249–322.
4. Huffman, J. W. *J. Org. Chem.* **1963,** *28,* 601, and references therein.
5. Berson, J. A. *Chemical Creativity. Ideas from the Work of Woodward, Huckel, Merweein and Others;* Wiley-VCH Verlag: Weinheim, Germany, 1999, Chapter 4: The Dienone-Phenol Mysteries. pp 77–107.
6. Santonin is commercially available from Aldrich (10 g, $24.20) or Sigma (10 g, $24.20; 50 g $107.20). At current prices each two-student setup use $1.21 worth or less of santonin.
7. The IR spectra were recorded on a Bruker IFS 25 as solids in KBr disks, and the NMR spectra were acquired on a Bruker AC-200-E in $CDCl_3$ solution (referenced to TMS) at 200.13 MHz for hydrogen and 50.33 MHz for carbon.
8. Moss, G. P.; Pregosin, P. S.; Randall, E. W. *J. Chem .Soc., Perkin Trans. 1* **1974,** 1525–1527.
9. Waring, A. J.; Zaidi, J. H.; Pilkington, J. W. *J. Chem. Soc., Perkin Trans. 1*, **1981,** 1454–1459.
10. Waring, A. J. *J .Chem .Soc. ,Perkin Trans. 2*, **1984,** 373–382.