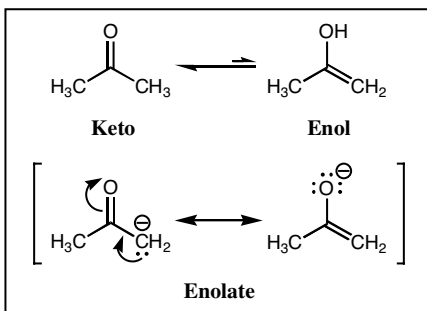


Outline & Study Guide for Unit VI. Enols & Enolates



In 1993 and 1994, a family of marine-derived natural products were isolated from three different sea sponges. Several of these natural products, including spongistatin 2 (altohyrtin C), exhibited **remarkable anti-tumor activity** when tested against the National Cancer Institute's panel of cancer cell lines. The spongistatins are believed to slow down tumor growth by inhibiting tubulin polymerization, and they appear to bind at a unique site at the tubulin dimer.

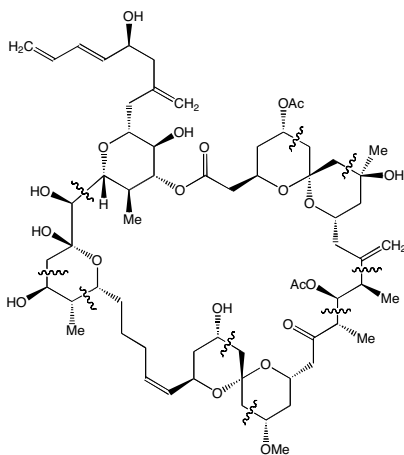


Figure 1
spongistatin 2 (altohyrtin C)

⋯ = Bond Formed Using Enolate Chemistry

Because of this noteworthy biological activity, there is a great deal of interest in probing the specific mode of action of the spongistatins. **The problem?** Very little of the active compounds can be isolated from the natural sources. In addition, although five different research groups had successfully synthesized a member of the spongistatin family by 2002, none of these syntheses generated more than **four milligrams** of the final product!

To overcome this problem, Professor Clayton Heathcock at the University of California, Berkeley set out to develop a synthesis that could generate multi-gram quantities of spongistatin 2. His final synthesis, published in September 2003 (*J. Am. Chem. Soc.* **2003**, *125*, 12844–12849), required a total of **113 steps** and generated **250 milligrams** of the natural product. While still far from the multi-gram goal, this quantity is more spongistatin 2 than has ever existed from the original isolation and all previous syntheses combined!

What does this have to do with enols and enolates? Professor Heathcock is one of the pioneers of enolate chemistry, and he used enolates to form many carbon–carbon bonds in his synthesis of spongistatin 2 (see Figure 1). This is not unusual. Enolate chemistry is one of the cornerstones of modern organic synthesis, and over the next couple of weeks you will learn about some ways to harness the immense synthetic power of the carbonyl group—both as a nucleophile and an electrophile.

VI. Enols and Enolates (Chapter 22)

A. Introduction

1. Tautomerization

B. Reactions of Enols & Enolates

1. α -Halogenation of Ketones

- a) Basic Conditions
- b) Haloform Test
- c) Acidic Conditions

2. α -Alkylation

- a) Enolate Formation with LDA
- b) Alkylation of Enamines
- c) Alkylation of β -Dicarbonyl Compounds

3. Aldol Condensation

- a) Acidic Conditions
- b) Basic Conditions
- c) Mixed Aldol

4. Claisen Condensation

- a) Dieckmann Condensation
- b) Crossed Claisen

5. Michael Reaction

- a) Robinson Annulation

6. Biosynthesis

Suggested Reading:

Chapter 22 (pp. 1003–1051)

Recommended Problems:

Chapter 22-2,7,13,17,19,24,31,32,
35,37,42,44,47,56,59,64,65

Extra Problems: (for more practice)

Chapter 22-8,11,16,20,23,26,33,38,
40,45, 48,66,68,69,76