# Topics in STEREOCHEMISTRY

N. L. Allinger, E. L. Eliel & S. H. Wilen
EDITORS

Volume 13

TOPICS IN

# STEREOCHEMISTRY

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# INTRODUCTION TO THE SERIES

During the past two decades several texts in the areas of stereochemistry and conformational analysis have been published, including *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965). While the writing of these books was stimulated by the high level of research activity in the area of stereochemistry, it has, in turn, spurred further activity. As a result, many of the details found in these texts are already inadequate or out of date, although the student in stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.

For both human and economic reasons, standard textbooks can be revised only at infrequent intervals. Yet the spate of periodical publications in the field of stereochemistry is such that it is an almost hopeless task for anyone to update himself by reading all the original literature. The present series is designed to bridge the resulting gap.

If that were its only purpose, this series would have been called "Advances (or "Recent Advances") in Stereochemistry." It must be remembered, however, that the above-mentioned texts were themselves not treatises and did not aim at an exhaustive treatment of the field. Thus the present series has a second purpose, namely, to deal in greater detail with some of the topics summarized in the standard texts. It is for this reason that we have selected the title *Topics in Stereochemistry*.

The series is intended for the advanced student, the teacher, and the active researcher. A background for the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental import aimed primarily at an audience of inorganic and organic chemists but involved frequently with fundamental principles of physical chemistry and molecular physics, and dealing also with certain stereochemical aspects of biochemistry.

It is our intention to bring out future volumes at intervals of one to two years. The editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of editorial advisers who have been of great assistance by suggesting topics and authors for several chapters and by helping us avoid duplication of topics appearing in other, related monograph series. We are grateful to the editorial advisers for this assistance, but the editors and authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

N. L. ALLINGER
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# PREFACE

Following publication of an entire volume (Volume 12) devoted to inorganic and organometallic stereochemistry it would be tempting to say that, with Volume 13, *Topics in Stereochemistry* returns to its more familiar format, namely, that devoted to organic stereochemistry. We wish to signal, however, that we expect to continue to present, at regular intervals, articles on stereochemical topics of interest to inorganic chemists and biochemists, as well as others. At the same time, we call attention to the fact that with this volume Professor Samuel H. Wilen of the City College, City University of New York, has become a regular co-editor of the series.

The first chapter in this volume is a particularly timely one given the recent surge of activity in natural product synthesis based upon stereocontrolled Aldol Condensations. D. A. Evans, one of the principal protagonists in this effort, and his associates, J. V. Nelson and T. R. Taber, have surveyed the several modern variants of the Aldol Condensation and discuss models to rationalize the experimental results, particularly with respect to stereochemistry, in a chapter entitled "Stereoselective Aldol Condensations." The authors examine Aldol diastereoselection under thermodynamic and kinetic control as well as enantioselection in Aldol Condensations involving chiral reactants.

The second chapter, by E. Ōsawa and H. Musso, is entitled "Application of Molecular Mechanics Calculations to Organic Chemistry." It describes the force field models presently in use as well as their scope and limitations. The authors survey the applications of these models to conformational analysis, to reaction mechanisms, to the analysis of NMR spectra, and to the design of medicinal agents.

M. V. Stewart and E. M. Arnett are the authors of the third chapter, "Chiral Monolayers at the Air–Water Interface." The chapter brings together the disciplines of surface chemistry and stereochemistry to demonstrate that the properties of stereoisomers may be useful in extending our understanding of the weak yet important intermolecular forces that operate in surface monolayers. The authors demonstrate that, in a complementary way, the techniques of surface chemistry make possible novel experiments that yield clear and

convincing evidence of intermolecular interaction that is stereochemically pertinent.

Because this area is not too well known, the authors have taken pains to describe, in some detail, experimental monolayer chemistry. The centerpiece of the chapter is enantiomer and diastereomer discrimination in monolayers. It concludes with a discussion of surface properties, in particular energetics, which are quite sensitive to stereochemistry. We call attention to the fact that this chapter is of potential interest to biochemists, notably those concerned with lipids and with cell membrane organization.

Configurational assignments and the determination of enantiomeric purity by NMR spectroscopy are techniques that are in frequent use by contemporary experimentalists. One of these techniques, involving Chiral Lanthanide Shift Reagents (CLSR) was surveyed in Volume 10 of this series. A complementary technique of earlier provenance applies "NMR Chiral Solvating Agents" (CSA) to these problems. The authors of this fourth chapter, W. H. Pirkle and D. J. Hoover, examine the nature of CSA-induced nonequivalence and survey the correlation of absolute configuration with a wide range of solvents. The limitations and exceptions to the models applied to the configurational assignments are carefully delineated. In addition, self-induced nonequivalence is described and a comparison is made between the CSA and CLSR techniques.

Organosulfur chemistry is presently a particularly dynamic subject area. The stereochemical aspects of this field are surveyed by M. Mikołajczyk and J. Drabowicz in the fifth chapter, entitled "Chiral Organosulfur Compounds." The synthesis, resolution, and application of a wide range of chiral sulfur compounds are described as are the determination of absolute configuration and of enantiomeric purity of these substances. A discussion of the dynamic stereochemistry of chiral sulfur compounds including racemization processes follows. Finally, nucleophilic substitution on and reaction of such compounds with electrophiles, their use in asymmetric synthesis, and asymmetric induction in the transfer of chirality from sulfur to other centers is discussed in a chapter that should be of interest to chemists in several disciplines, in particular synthetic and natural product chemistry.

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# TOPICS IN STEREOCHEMISTRY

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# CONTENTS

# Stereoselective Aldol Condensations*

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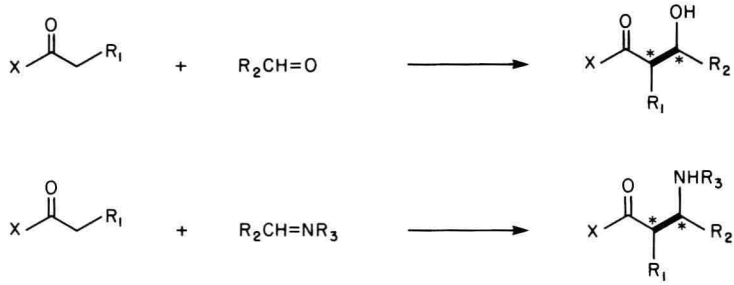
*Contribution No. 6437 from the Laboratories of Chemistry, California Institute of Technology.

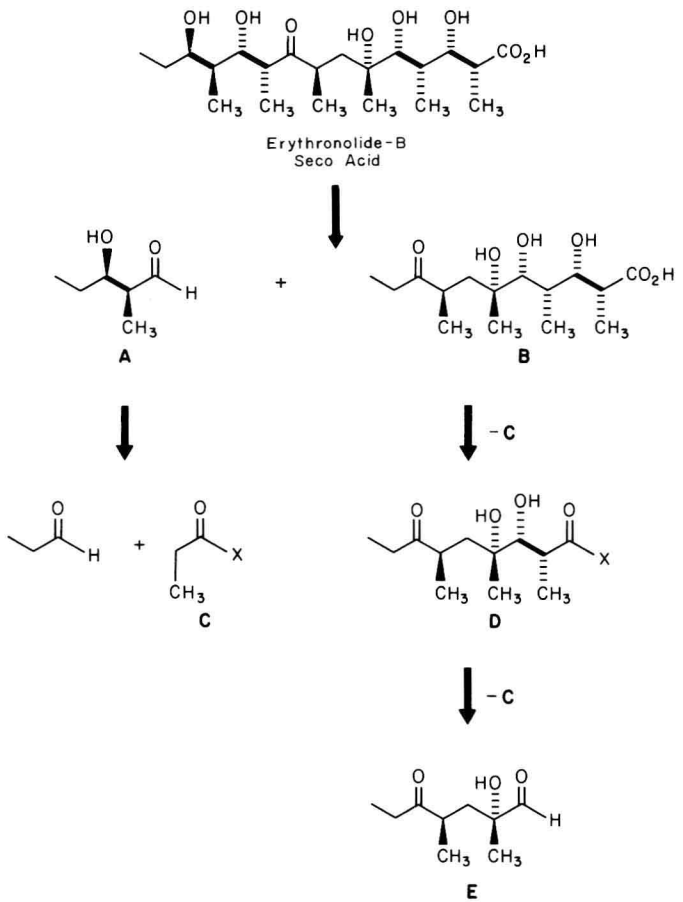
## I. PROLOGUE

The aldol process constitutes one of the fundamental bond constructions in biosynthesis. This reaction, along with related variants involving Schiff bases, is among the oldest classes of reactions in organic chemistry and is well recognized as the most obvious bond

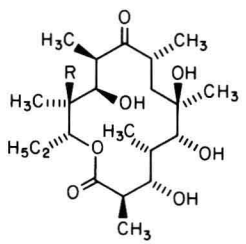



construction for the creation of 1,3-*O,O* and 1,3-*N,O* heteroatom-heteroatom relationships in organic molecules. In recent years the macrolide and ionophore antibiotics have been generally recognized as viable targets for total synthesis. Because the aldol process is intimately involved in the biosynthesis of these classes of molecules, there has been a renewed interest in the development of stereoregulated aldol condensations that might be applied to the efficient synthesis of such target structures. The erythromycin aglycones, erythronolide A (R = OH) and erythronolide B (R = H) illustrate the prominence of the aldol process in the biosynthesis of these structures. An examination of the erythronolide B seco acid (Scheme 1) reveals the four obvious aldol disconnections illustrated wherein the propionate subunit C might be perceived to be involved in three of the four condensations with the possible generation of eight of the ten required asymmetric centers.

The major obstacle confronting the implementation of such "biomimetic" syntheses has been associated with the stereochemical aspects of the aldol process. Over the past few years considerable progress has been made in the development of stereoregulated aldol condensations. This chapter attempts to survey this aspect of the topic. For a more general treatment of the subject the reader is referred to several other excellent reviews (1).

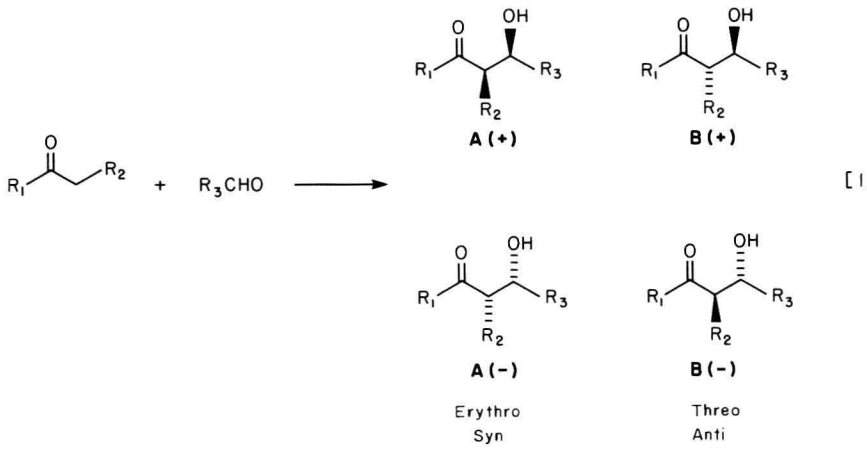

Erythronolide-B
Seco Acid
A
B
C
D
E
-C
-C

Scheme 1


R = OH, Erythronolide A
R = H, Erythronolide B

## II. INTRODUCTION

In the crossed aldol condensation between carbonyl partners there are four possible product stereoisomers (eq. [1]). Consequently, there are two stereochemical aspects associated with the reaction: The first deals with internal stereochemical control or *diastereoselection* [A(±) vs. B(±)], and the second deals with absolute stereochemi-

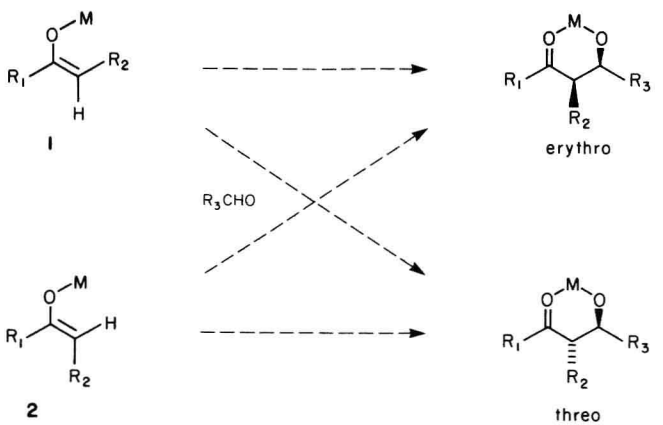



[1]

cal control for a given diastereomer or *enantioselection* [A(+) vs. A(–) or B(+) vs. B(–)]. With regard to the diastereomer nomenclature, two conventions are now in existence. The widespread practice of referring to **A** and **B** as the erythro and threo diastereomers, respectively, is not rigorously correct for *all* possible structural permutations of $R_2$ and $R_3$ and has caused some confusion. This issue has recently been addressed by both Heathcock (2) and Masamune (3) within the context of the aldol problem. Given the extended or "zigzag" conformation of the carbon backbone containing the relevant functions (=O, OH) as illustrated, that diastereomer, **A**, disposing the substituents $R_2$ and OH in a gauche relationship, has been defined as either the erythro (2) or the syn diastereomer (3). In an analogous fashion, isomer **B** has been defined as either the threo or the anti diastereomer. Because of the popularity of the erythro-threo convention, its usage is continued in this discussion in the context of the foregoing definition.

In principle, stereoselective aldol condensations can be carried out under two distinct sets of conditions. Under the influence of acid catalysis, stabilized enol derivatives of defined geometry (M = $SiMe_3$,

alkyl) can be induced to condense with aldehydes and acetals in a stereoselective fashion (4). However, data accumulated on the acid-catalyzed aldol variants to date have been insufficient to permit detailed speculation on the possible transition state control elements responsible for kinetic aldol diastereoselection. Alternatively, the same process can be carried out directly with aldehydes ($R_3CHO$) and preformed metal enolates (M = Li, MgL, ZnL, $AlL_2$, $BL_2$, etc.) of defined geometry (eq. [2]). In kinetically controlled condensations there now exists an abundant body of data that correlates aldol product stereochemistry to enolate geometry (2,5,6). This aspect of the topic is treated in detail. With regard to enolate stereochemical nomenclature, the structures 1 possessing a syn stereochemical relationship between the enolate ligand $R_2$ and oxygen substituent (OM) will be referred to as (*Z*)-enolates. In a similar fashion the anti stereochemical relationship between $R_2$ and OM as in 2 will be designated as the (*E*)-enolate.




[2]

## III. ALDOL STEREOCHEMICAL ASSIGNMENTS

One of the most popular spectroscopic methods for the assignment of aldol stereochemistry is proton (nuclear) magnetic resonance ($^1$H NMR) spectroscopy (7). In many instances erythro-threo stereochemical assignments may be conveniently made from the magnitude of the vicinal coupling constant $J_{AB}$. When intramolecular hydrogen bonding provides the dominant conformational bias ($K < 1$) $J_{AB}$ (erythro) falls in the approximate range of 3 to 6 Hz, and $J_{AB}$ (threo)