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Stereoselective Synthesis (Part F)

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edited by Atta-ur-Rahman

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Studies in Natural Products Chemistry

Volume 10

Stereoselective Synthesis (Part F)

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FOREWORD

Nature manifests its glorious wonders in many beautiful ways. Organic molecules are the raw material from which the strangest phenomenon of all - life - is constructed. It is therefore not surprising that organic chemistry has attracted some of the foremost organic chemists, and the field of stereoselective synthesis of complex natural products has taxed their ingenuity to develop shorter and more attractive routes to these challenging substances.

The present volume is the tenth of the series and it again features contributions by leading exponents in the field of organic synthesis. Review articles on the synthesis of cembranes, vitamin D, isoquinolinequinone antibiotics, medium ring ethers, didemnins, C-glycosides, blood group I and i active oligosaccharides, glycosidase and glycosyl transferase inhibitors, novel nucleosides, macrocyclic oligopeptides and chiral alkaloids should provide a wealth of information to a large number of organic chemists. Articles on additions to polyunsaturated carbonyl compounds, novel ring transformations and Claisen rearrangements applied to carbohydrate precursors should provide organic chemists with stimulating reading material.

It is hoped that these contributions by a distinguished group of organic chemists would be received with the same enthusiasm as the previous volumes of this series. That the 10th volume is being published within 3 1/2 years of the publication of the first volume reflects the world-wide interest in this series, and I wish to express my sincere thanks to the support and encouragement which I have received from distinguished colleagues.

I would like to express my thanks to Dr. Zahir Shah, Mr. Ejaz Ahmad Soofi, Dr. Miss Khurshid Zaman and Miss Anis Fatima for their assistance in the preparation of the index. I am also grateful to Mr. Kamran Faisal Khan and Mr. Asif Mehmood Raja for typing and Mr. Mahmood Alam for secretarial assistance.

December 1991

Atta-ur-Rahman,
Editor

PREFACE

Organic chemistry evolved from man's desire to understand the basic building blocks of living systems. Thus, investigations into the chemistry of natural products constituted the birth of the discipline. Berzelius in 1806 published his "Lectures in Animal Chemistry" in which he stated "the part of physiology which describes the composition of living bodies and the chemical processes which occur in them is termed organic chemistry". Nearly two hundred years later, the challenges of natural products remains undiminished, not because of the lack of progress but because the successes that have been achieved have opened ever more opportunities.

Volume 10 of the series "Studies in Natural Products Chemistry" edited by Atta-ur-Rahman provides an insight into some of the exciting contemporary problems. The volume focuses on the synthetic challenges offered by diverse classes ranging from terpenes to nucleosides. The basic methodology defines what targets are accessible. Thus, it is appropriate to dedicate several chapters to the development of new reactions expanding our repertoire of synthetic methods. Chapters that define new reaction concepts not directly tied to any specific class of natural products to those that have their stimulus from specific classes such as macrocycles or oxapolycycles are both included. From synthetic methodology emanates synthetic strategy. The combination of the Claisen rearrangement with substrates from the "chiral pool" appropriately illustrates this natural flow.

The bulk of the chapters illustrate the synthetic challenge of a particularly important molecule, e.g. Vitamin D, or a specific class. From the diverse opportunities for application of methods of macrocarbocycle construction represented by the cembranes to macroheterocycles such as the cyclic peptides we see the barrier for attacking such problems at a chemical level fall opening the prospect for collaboration with biologists to better understand and define their myriad of biological roles from being antibiotic to antitumor agents. Carbohydrates and nucleic acids have been categorized as specialized fields unto their own and apart from the traditional classes of compounds considered fair game for the natural products' chemist. No longer. They represent not only the most abundant natural products but also the most important. Tremendous strides in our ability to approach these compounds chemically is opening vast vistas in terms of their biological consequences. To have all of these themes treated in this one

volume provides exciting reading and an opportunity to marvel at how far we have come. Most importantly, it also shows us how far we yet have to go.

Two centuries from now we may still marvel at how much opportunity and challenge natural products' chemistry may hold for us.

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Palo Alto
December 14, 1991

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Stereoselective Synthesis

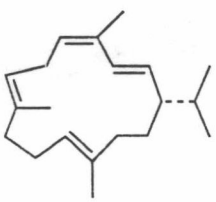
Atta-ur-Rahman (Ed.), *Studies in Natural Products Chemistry*, Vol. 10

Studies on the Synthesis of Cembranes

James Arthur Marshal

1. INTRODUCTION

The family of diterpenes, now known as cembranes, was first elucidated in 1962 when two groups, working independently, reported the structure of a hydrocarbon **1** isolated from pine oleoresin.[1,2] A third group, that same year, described a structurally related pair of isomeric diols **2** and **3**, of unknown stereochemistry, from tobacco plants.[3] The nearly simultaneous discovery of



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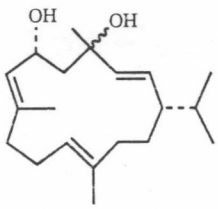
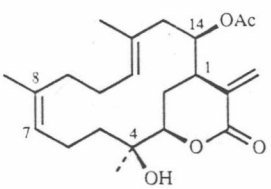


2 α-OH
3 β-OH

a new family of natural products by three independent groups caused some initial confusion in nomenclature and structural representation. Thus, the names "cembrane"[1] and "thunbergane"[2] were both proposed for **1** and the diols **2** and **3** were named as derivatives of the hypothetical parent hydrocarbon "duvane."[3] Eventually, the name "cembrane" was adopted for the family.[4] In the early years several different structural representations were used for cembranes. Attempts to depict the 14-membered cembrane ring with the hexagonal template familiar to organic chemists led to errors in stereochemical assignments. Figure 1 shows four of the more common representations for the marine cembranolide crassin acetate.[5] Note that **4** and **5** erroneously depict the 7,8 double



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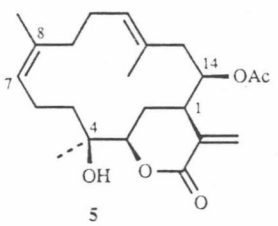

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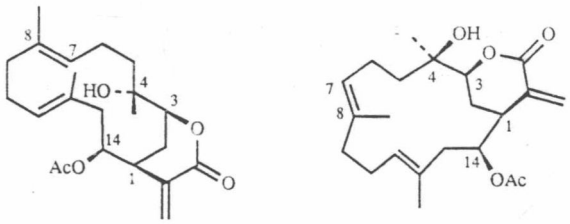
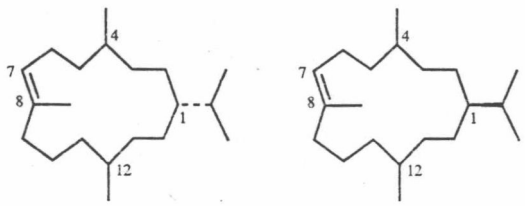
Figure 1. Structural representations for crassin acetate.



6 7

Figure 1. Structural representations for crassin acetate. (continued)

bond as (Z). In addition, the stereocenters at C1, C3, C4 and C14 are enantiomeric in **4/5** *vs* **6/7**. Furthermore, because of the differing projections, the oxygens at C3 and C4 appear to be anti in **6** and syn in **7**. In 1977 Weinheimer, *et al.* advocated the now familiar template **8** for the cembrane ring system.[6] The almost universal presence of an (E)-double bond or *trans* epoxide at C7/C8 enables a stereochemical distinction to be made between **8** ("α-series") and its enantiomer **9** ("β-series").

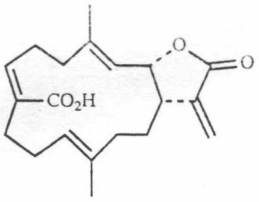


8 α-series **9** β-series

2. NATURAL OCCURRENCE AND BIOACTIVITY

In the past three decades hundreds of cembranes have been found in Nature. Tobacco and soft coral are particularly rich sources of these materials.[4] The bioactivity of cembranes has not been extensively studied. Most of the marine derived cembranoids are toxic to fish.[7] Crassin acetate (**7**) possesses antimicrobial and antiprotazoal activity.[8, 9] It has also been found to lower blood pressure and cause smooth muscle relaxation in the guinea pig.[10] It is cytotoxic against human leukemic cells and shows antineoplastic activity toward lymphocytic leukemia.[11]

Recently, the diastereomeric cembratriene-4,6-diols α-CBT (**2**) and β-CBT (**3**) have been found to inhibit the early antigen of Epstein-Barr virus induced by phorbol esters.[12] These cembrenes also showed marked inhibition of skin tumors initiated with 7,12-dimethylbenz[a]-anthracene and promoted by phorbol esters.[12] The cembranolide lobohedleolide (**10**) showed similar activity. Sarcophytol B (**11**), a structural isomer of α- and β-CBT, likewise inhibits tumor promotion by teleocidin on mouse dorsal skin.[13] Sarcophytol A (**12**) has recently been shown to arrest cancer development in the large bowel of rats.[14]



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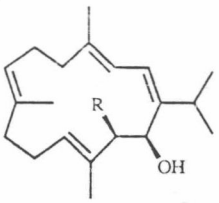
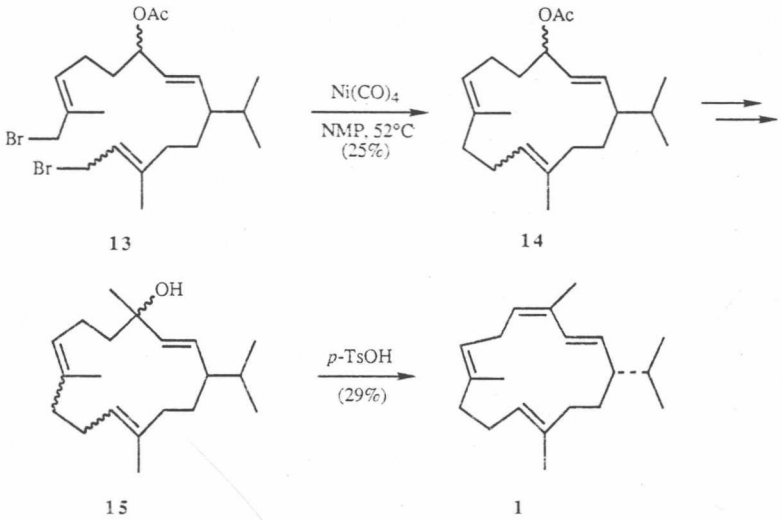


11 R = OH
12 R = H

3. SYNTHESIS

3.1 *Structure Confirmation*

The first synthesis of a natural cembrane was achieved by Dauben and co-workers in 1974.[15] At the time few methods were available for the closure of medium or large ring carbocycles. Using methodology developed by Corey for cyclic 1,5-dienes,[16] Dauben was able to cyclize dibromide **13** in 25% yield. Dehydration of the derived allylic alcohol **15** with *p*-TsOH afforded a mixture of six hydrocarbons from which crystalline (±)-cembrene (**1**) could be isolated



13 14

15 1

by chromatography on $AgNO_3$-impregnated silica gel. In subsequent years considerable effort has been devoted to cembrane synthesis.[17,18] In this chapter we will present an overview of synthetic approaches developed in our laboratory over the past ten years. A recent review by Tius summarizes synthetic work to 1987 with particular emphasis on ring closure methodology. More recent synthetic achievements are listed in footnote 18.