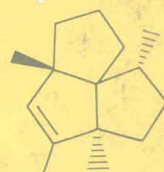
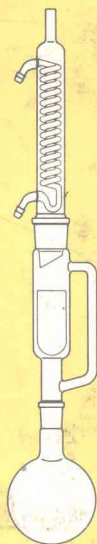


Studies in Natural Products Chemistry

Atta-ur-Rahman/Editor



Volume 3

Stereoselective Synthesis (Part B)

Elsevier

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**Studies in
Natural Products Chemistry**

Volume 3

Stereoselective Synthesis (Part B)

Studies in Natural Products Chemistry
edited by Atta-ur-Rahman

Vol. 1 Stereoselective Synthesis (Part A)

Vol. 2 Structure Elucidation (Part A)

Vol. 3 Stereoselective Synthesis (Part B)

FOREWORD

The spectacular developments in the field of natural products chemistry during the last few decades have been triggered by a growing understanding of organic reaction mechanisms and by the enormous advances in technology. The field of stereoselective synthesis of complex molecules has posed a constant challenge to organic chemists, and natural products, with their wide diversity of complex structures and biological properties, have been a natural target for such efforts. This book is the third volume of the series Studies in Natural Products Chemistry and the second one devoted to the area of stereoselective synthesis. It reviews and highlights the important contributions made by eminent scientists. It is hoped that the articles contained in this volume, which cover a wide variety of organic reactions and strategies to the stereoselective synthesis of complex structures will provide stimulating reading to a large number of synthetic organic chemists.

I wish to express my thanks to Miss Khurshid Zaman for her assistance in preparation of the index and Mr Mahmood Alam for secretarial assistance.

November 1988

Atta-ur-Rahman, Editor

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Stereoselective Synthesis

SYNTHESIS OF NATURAL PRODUCTS CONTAINING FIVE-MEMBERED RINGS. AN EVOLUTION OF GENERAL METHODOLOGY

TOMAS HUDLICKY,* FAN RULIN, THOMAS C. LOVELACE, AND JOSEPHINE W. REED

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- 1.1 Introduction
- 1.2. Total Synthesis of Triquinanes
 - 1.2.1. Triquinane terpenes. An overview of synthetic approaches
 - 1.2.2. Topological analysis of triquinane synthesis
 - 1.2.3. Intramolecular [4+1] annulation via diene–carbenoid additions
 - 1.2.4. Total synthesis of triquinanes by [4+1] annulation
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- 1.5. Summary and conclusion
- 1.6. Acknowledgments
- 1.7. Tabular survey of total syntheses
- 1.8. References

1.1. INTRODUCTION

The synthesis of compounds containing rings composed of an odd number of atoms has traditionally been far less successful than the preparation of their even-numbered cousins. This statement is reinforced by the observation of some of the elements of synthetic design that are required before any preparative venture begins (ref.1). This chapter will address some developments in the area of five-membered ring synthesis and discuss concepts that govern such an undertaking. The first of these, and undoubtedly the most important, is the concept of charge

parity termed either synthetic consonance (for electrostatically balanced systems) or dissonance (for those systems where two like latent charges must be adjacent to one another) (ref. 2). Naturally, the physical impossibility of a consonant relationship in any five-membered ring makes its design a less feasible task than the corresponding assembly of six-membered systems. The second problem lies in the absence of reliable methods available to predict stereoelectronic trends in these compounds because the ideal tetrahedral angles are distorted when compared to the cyclohexane-type systems. This angular distortion also complicates the spectral analysis of such structures as most methods are derived from strain-free cyclohexanes. The third complication seems to stem from the lack of synthetic methods available for the construction of five-membered ring compounds in a manner independent of their substitution pattern or the number and disposition of any heteroatoms. Most general methodologies lack the versatility and the vehemence of the processes employed routinely in the synthesis of six-membered ring compounds. Traditional methods as powerful as the Diels–Alder reaction or the Robinson annulation do not have equivalents in the cyclopentanoid field, yet these methods can be adapted to accommodate virtually every combination of heteroatoms imaginable.

The mission of this chapter is the presentation of those accomplishments that address the problem of general and systematic synthetic design for five-membered ring compounds in the context of a system-oriented approach to naturally occurring substances. These accomplishments will be summarized in terms of topological comparison with the preparation of six-membered ring compounds (ref. 3). The presentation will highlight the evolution of some general methods of synthesis and also provides an overview of current accomplishments in the field of triquinane synthesis.

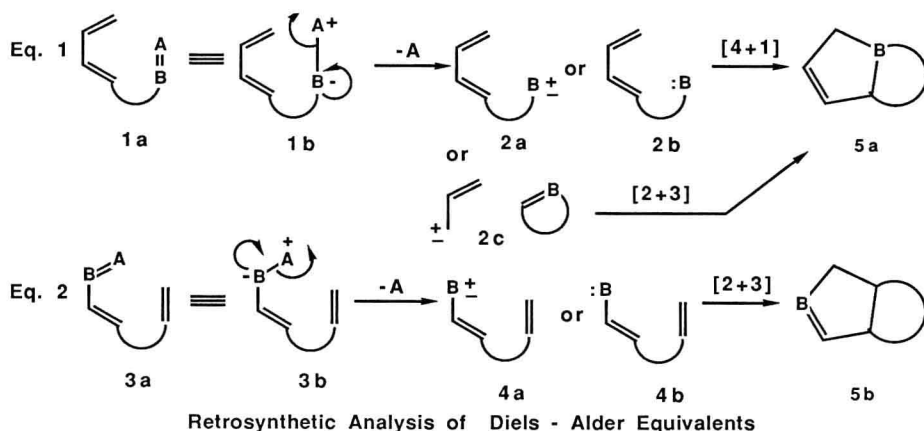


Figure 1.

To approach a general design of five-membered ring compounds, we initially examined the possibility of adapting the Diels–Alder reaction to the construction of five-membered rings as

shown in Fig. 1. Equation 1 shows an intramolecular Diels–Alder reaction in which the terminal atoms of the incipient six-membered ring would be excised in either a homolytic or a heterolytic sense to arrive at equivalents **2a** or **2b**, whose closure would provide a formal [4+1] annulation to give **5a**. Similar excision of the terminal atom in the diene system provides, through the depicted disconnection, the synthons **4a** and **4b**, whose ring closure also furnishes the cyclopentene annulated system **5b** via [2+3] annulation (Fig. 1). An additional approach to **5a** would become available via **2c**, an intermolecular variant of [2+3] annulation. (See section 1.2.5.) These disconnection philosophies represent the main avenues of cyclopentane synthesis and are applicable to the synthesis of heterocycles as well if a heteroatom is placed either on the diene or the atom **B**. The above derivation therefore conceptually provides an odd-carbon equivalent for the Diels–Alder cycloaddition via either [4+1] or [2+3] processes.

The ensuing discussion furnishes an overview of applications of these processes and any of their analogies to the synthesis of triquinane sesquiterpenes, pyrrolizidine alkaloids, and furanoid compounds to illustrate the potential for system-oriented design of classes of compounds. The presentation of the development of these powerful techniques is made in the order that the methods themselves have evolved. In order to begin the discussion of the development of the [4+1] and the [2+3] annulative processes, a literature review of those methods that addresses a generalized synthetic design for triquinane sesquiterpenes will be presented. It will be seen that some of these methods possess topological concepts similar to those that led to the design and the implementation of our methodology.

1.2. TOTAL SYNTHESIS OF TRIQUINANES

There are about forty different terpenes that can be termed triquinanes and these are shown in Table 1 and Table 2. Although the first member of this unique class of sesquiterpenes, retigeranic acid (**6**), was isolated eighteen years ago (ref. 4), the field of triquinane synthesis did not develop until the late seventies and early eighties, with hirsutic acid (**42**) being the first triquinane synthesized (ref. 5). The tabular survey at the end of this chapter shows a fascinating number of syntheses of this class of compounds. Perhaps more than any other discipline of organic

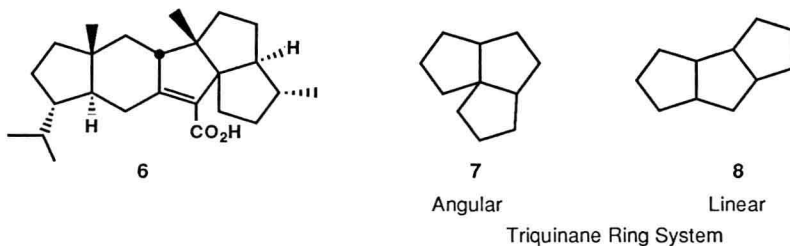


Figure 2.

TABLE 1. Angular Triquinanes

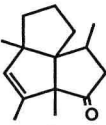
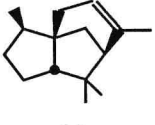
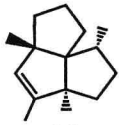
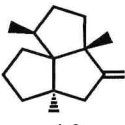
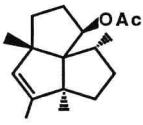
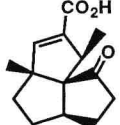
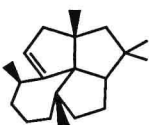

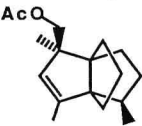
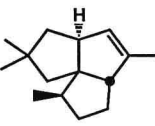
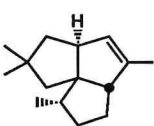
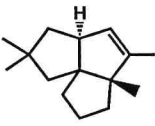
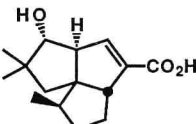
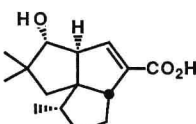
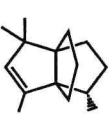
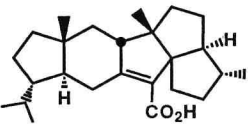
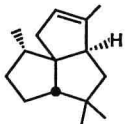

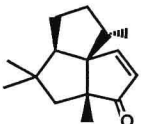
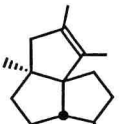
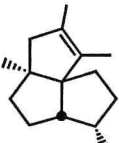
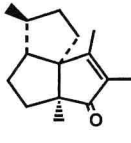
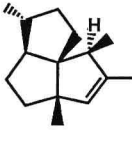
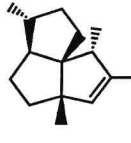
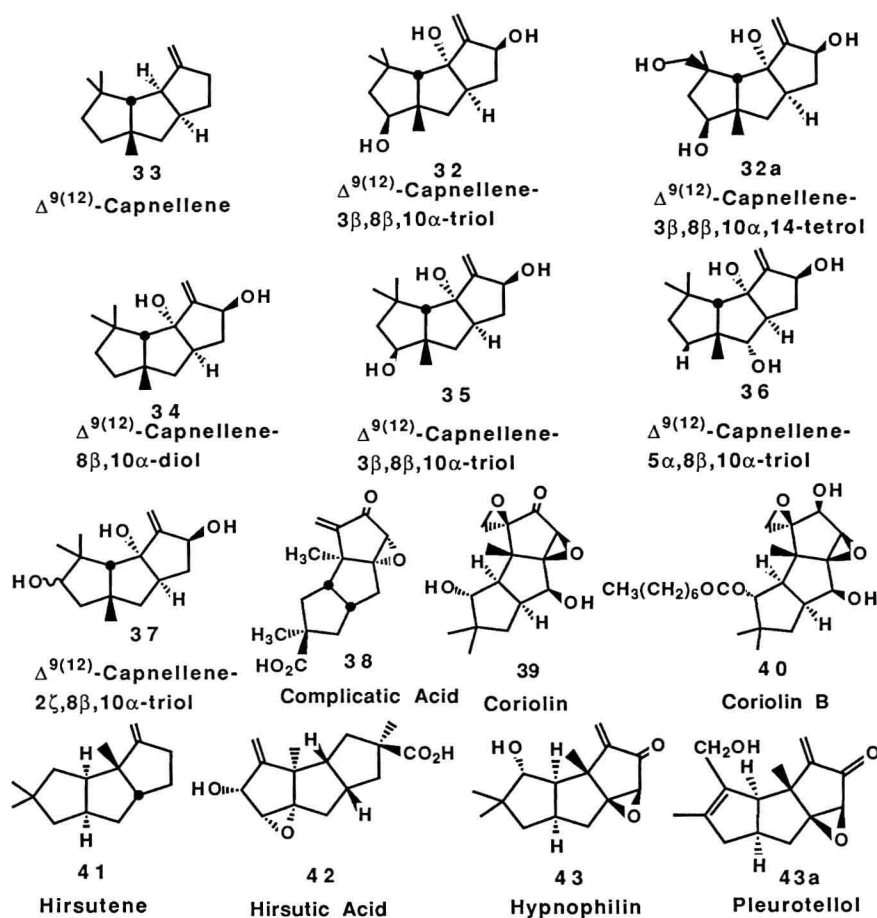
			
9 Arnicenone	10 Cedrene	11 Isocomene	12 β -Isocomene
			
13 1-Acetoxyisocomene	14 Subergorgic acid	15 Laurenene	16 Modhephene
			
17 13-Acetoxy modhephene	18 Pentalenene	19 Epipentalenene	20 Isopentalenene
			
21 Pentalenic Acid	22 Epipentalenic Acid	23 Epimodhephene	6 Retigeranic Acid
			
24 Senoxydene	25 Silphinene	26 3-Oxosilphinene	27 Silphiperfol-6-ene
			
28 9-Epi-silphiperfol-6-ene	29 5-Oxosilphiperfol-6-ene	30 7 α H-Silphiperfol-5-ene	31 7 β H-Silphiperfol-5-ene

TABLE 2. Linear Triquinanes



synthesis, the field of triquinane synthesis exploded into an area that served as testing grounds for cyclopentanoid synthetic methodology, as the prerequisite for a successful construction of the triquinane skeletons **7** or **8** must be a working method of functionalized cyclopentane synthesis. There has been a tremendous number of annulation techniques reported for units containing cyclopentane, cyclopentanone, cyclopentenone, cyclopentenol, etc., and these have been carefully reviewed (ref. 6). Similarly the synthetic approaches to triquinanes have been reviewed on several occasions (ref. 7). The approaches to triquinane skeletons that have evolved from the cyclopentanoid annulation schemes are numerous, and those approaches that can successfully be used for the construction of either angular or linear triquinanes will be summarized and related in their concepts.