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PREFACE

The field of natural product chemistry continues to attract the attention of some of the foremost chemists today. The vast diversity of natural Products available from the plant and animal kingdoms offers an unlimited source of novel compounds, many of which can find potential applications in medicine. Natural product chemistry has evolved with growing emphasis on isolating bioactive natural compounds. The synthetic programs are similarly directed towards bioactive natural products, many of which have been hitherto obtainable only in small quantities from natural resources, in much larger quantities by synthesis or by preparing new analogues which will have a higher activity and lower toxicity than the parent compounds. The present volume, which is the 13th in the series, specifically covers the field of such bioactive natural products and presents research being carried out on a wide variety of compounds including fungal metabolites, anti-cancer alkaloids, oligonucleotides, bioactive terpenes, anti-tumor antibiotics, cytochalasans, indole alkaloids, flavors, biologically active carba-sugars, etc. The in-depth presentations on some of the current frontiers of natural product chemistry should prove to be of wide interest.

We wish to express our sincere thanks to Dr. Zahir Shah, Miss Farzana Akhtar and Mr. Ejaz Ahmad Soofi for their assistance in the preparation of the index. We are also grateful to Mr. Waseem Ahmad and Mr. Habib Alam for typing, Mr. Mahmood Alam for secretarial assistance and Ms. Barbara Castagna of Abbott Laboratories for her assistance in preparing this volume.

ATTA-UR-RAHMAN
FATIMA Z.BASHA

FOREWORD

The synthesis of natural products has long fascinated organic chemists and has provided the perfect challenge to, and test of, their steadily developing synthetic powers. One attraction of this area of synthesis is the knowledge that the target molecules can be built, since obviously they have been constructed step after step by the biosynthetic machinery of the micro-organism or plant or animal. These synthetic transformations in living systems show exquisite control of regio-, chemo-, and stereo-selectivity and these are the standards to which we as synthetic chemists strongly aspire. In fact, enormous progress has been made. It is not a vast age ago, about forty years or so, that a successful synthesis was one which produced the right product even though in many cases one could not avoid the production of isomers and substantial quantities of by-products. Gradually the ability grew to assert control over reactions and especially over regio-chemistry and stereochemistry. Hand in hand, and increasingly over recent times, came delightful developments allowing control of the configuration of newly generated chiral centres. This phase largely involved stoichiometric methods at first but steadily over the last years, catalytic approaches have been developed. Enantioselection approaching that of enzymes is now being reported with accelerating frequency and this trend is certain to continue.

The present volume collects together a wide range of contributions which illustrate many of the recent developments I have alluded to already. The topics encompass the chemistry *inter alia* of terpenes, alkaloids, flavours, microbial metabolites including antibiotics, nucleotides, amino acids and carbohydrates. It is a varied feast and each chapter is written by chemists who are authorities in their chosen fields. No narrow view is taken and we see chapters covering the use of enzymes in synthesis, one on the biological effects of natural products and a third giving a broad survey of pharmacognosy. These complement the majority of the chapters which deal mainly with synthetic problems.

Surely this book will be read with benefit and pleasure by any red-blooded organic chemist. It is also certain that students will learn much from it and for teachers, it provides a supermarket of examples for synthetic course work. So this broad survey of topics is particularly welcome.

Cambridge
12 November 1992

Alan Battersby

Professor Sir Alan Battersby

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Bioactive Natural Products

Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 13*

Synthesis of Di- and Triquinane Sesqui-,di- and Sesterterpenes----Columbus Style

Leo Armand Paquette

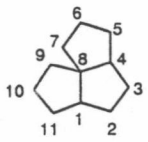
The discovery of the steroids, the recognition of their central role in the life process, and the identification of their modes of action contributed to the enormous synthetic effort dedicated to this class of molecules for several decades. As a result, synthetic methods suited to the elaboration of polycyclic six-membered ring systems were developed. The most well known of these constructions is the Robinson annulation reaction [1].

Approximately fifteen years ago, we became aware that the characterization of polyquinane molecules from natural sources was being reported at increasingly frequent intervals. Since very little was known at that time about the rational, mechanistically-based design of polycyclopentanoid compounds with suitable control of stereochemistry [2], we initiated synthetic activity in this area. The considerations that prompted our entry into polyquinane natural products chemistry have proven attractive to many research groups in the intervening years. As a consequence, an impressive array of methods for preparing fused polycyclopentanoid systems is now available [3]. In fact, this activity can be singled out as one of the most dynamic and imaginative undertakings in synthetic organic chemistry in the last decade.

The studies to be described herein were formulated in order to gain access to a number of the terpenoids that fit the polyquinane description. To be sure, many related achievements deserve to be recognized. However, space requirements dictate that the present chapter be confined to those developments arising from research undertaken at The Ohio State University. The overview will focus initially on angular triquinanes, progress to more highly oxidized congeners of these systems, present those tactics associated with linear and propellane triquinane synthesis, and conclude with an examination of routes to structurally related substances.

A. ANGULAR TRIQUINANES

The carbocyclic cores of the triquinane sesquiterpenes feature either the tricyclo[6.3.0.$0^{4,8}$]undecane (**1**), tricyclo[6.3.0.$0^{3,7}$]undecane (**2**), or [3.3.3]propellane network (**3**). The serial fusion of three five-membered rings in



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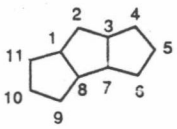

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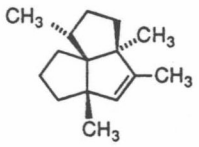
the second instance has caused compounds of this class to be designated as linear triquinanes. Molecules of type **1** are commonly referred to as angular triquinanes. All three groups have served as enormously fertile testing grounds for the development of useful new synthetic reactions.

1. Isocomene. The sesquiterpene hydrocarbon **4**, known as isocomene, was independently isolated by two groups in 1977 [4,5]. Although **4** contains four



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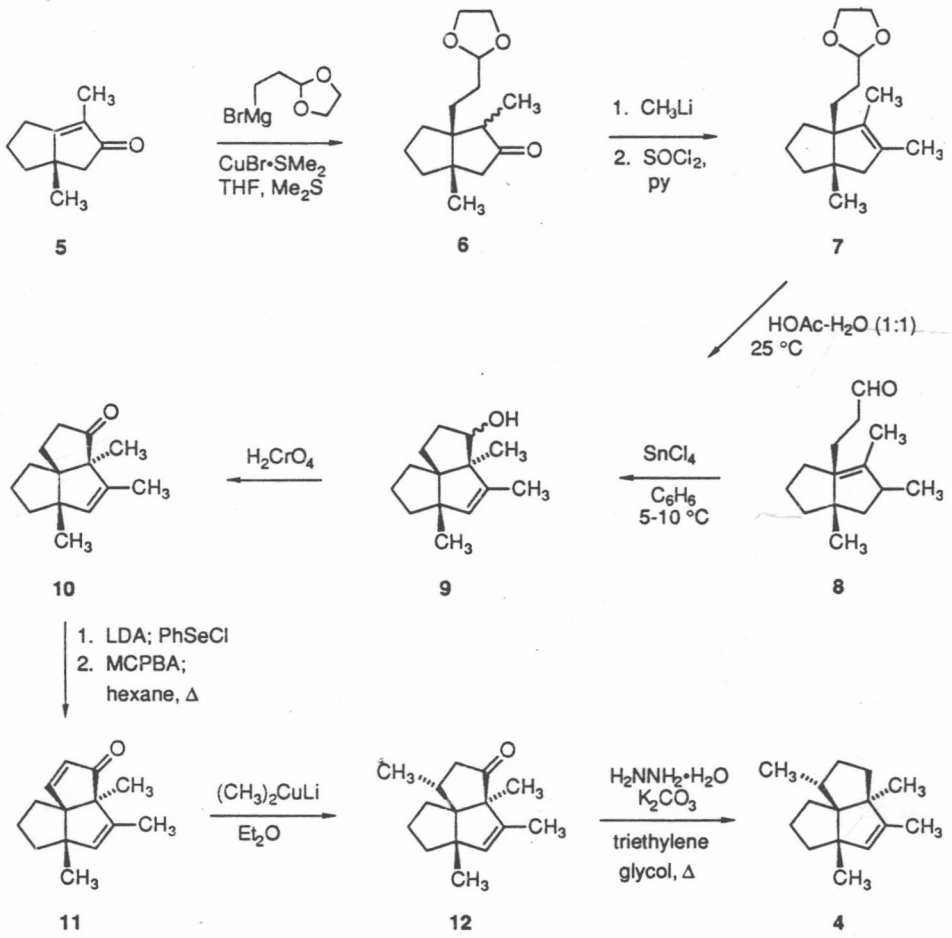
contiguous stereogenic centers, the location of three of these carbon atoms at points of ring fusion was certain to reduce complexity dramatically. From the outset [6], our plan for the construction of this target was to take advantage of an attractive cyclopentannulation protocol that had just been devised by Marfat and Helquist [7]. For this purpose, bicyclic enone **5** was required and this intermediate was produced on large scale by Yoshikoshi's direct route [8]. When **5** was exposed to the magnesio cuprate derived from β-bromopropionaldehyde ethylene ketal, conjugate addition occurred smoothly to provide **6** (68%, Scheme I). Entry cis to the angular methyl group was mandated by steric accessibility to the β face and by the significantly greater thermodynamic stability of cis-bicyclo[3.3.0]octanes relative to their trans isomers [9]. The stereochemical inhomogeneity of the α-carbonyl site was of no consequence since it was soon to be rectified.

In order to explore the merits of the latent aldehyde functionality as an initiator of ring cyclization, **6** was treated with methyllithium and the tertiary carbinol so produced was directly dehydrated (79%). In sterically hindered cyclopentanones such as **6**, Grignard-induced enolization can prove to be a serious complication. This issue was conveniently skirted by repeated sequential exposure to CH_3Li and methanol (1 equiv) prior to workup. Furthermore, the use of thionyl chloride in pyridine as the dehydrating agent resulted in exclusive introduction of the more highly substituted double bond.



5 **6** **7** **8** **9** **10** **11** **12** **4**

Scheme I

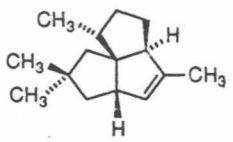
Subsequent mild hydrolysis of **7** in aqueous acetic acid at room temperature resulted in the formation of both aldehyde **8** (62%) and tricyclic alcohol **9** (19%). These results served as an early indication of the facility with which **8** enters into ene-type cyclization [10]. When this closure was performed independently in the presence of stannic chloride, the conversion did indeed prove to be highly efficient (95%) and nicely regiocontrolled.

With an efficient approach to **9** available, the stage was set for oxidation to **10** (77%) and introduction of an α,β-unsaturated double bond by means of organoselenium technology [11] (88%). At this point, the high conformational rigidity of **11** and the approximate planarity of its cyclopentenone ring were revealed by the rather disparate chemical shifts of the α (δ 5.94) and β (δ 7.31) protons in $CDCl_3$ solution.

From a tactical viewpoint, the nonangular methyl substituent remaining to be introduced can be seen to reside on the less encumbered surface of the five-membered ring to which it is bonded. In agreement with the principles of steric approach control, lithium dimethylcuprate condensed with **11** to deliver only **12**, direct reduction of which under modified Wolff-Kishner conditions [12] produced isocomene in 80% overall yield for the two steps.

As will become apparent, the cyclopentannulation approach constitutes a reliable tool for the expedient synthesis of structurally more elaborate angular triquinanes.

2. Pentalenene. The least oxidized precursor to the pentalenolactone class of antibiotics has been identified as pentalenene (**13**) [13]. Produced by the



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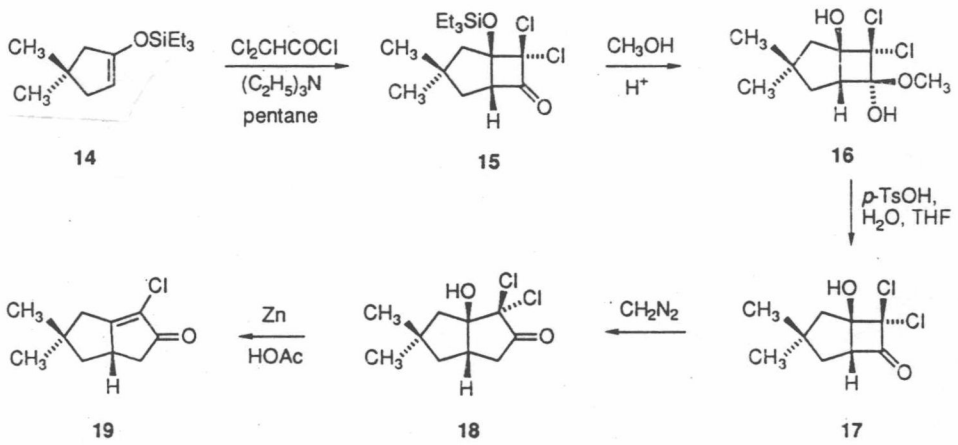
cyclization of humulene, this sesquiterpene is also related biogenetically to the illudoids [14], the coriolins [15], marasmic acid [16], and fommanosin [17], very likely by means of the protoilludyl cation [18].

Careful analysis of the structural features of **13** led to the decision to proceed via the bicyclic chloro enone **19** (Scheme II) [19]. To this end, silyl enol ether **14** was engaged in a [2+2] cycloaddition with dichloroketene with the expectation that the usual regioselectivity observed for such reactions [20]

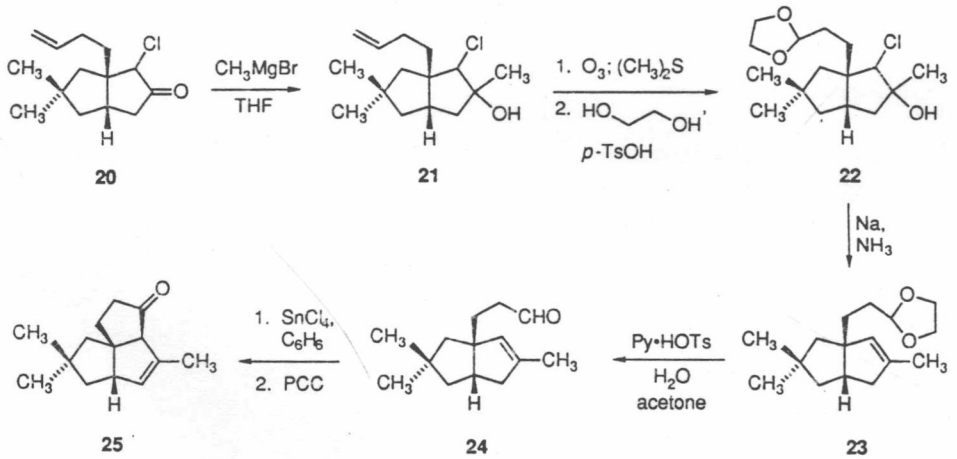


14 **15** **16** **17** **18** **19**

Scheme II

would be adhered to. Indeed, cyclobutanone **15** was uniquely produced (83%). When dissolved in acidic methanol, this sensitive intermediate was transformed into hemiketal **16**, a stable and relatively nonvolatile substance from which admixed Et_3SiOMe could be removed in vacuo. The issue of ring expansion was explored following the liberation of **17**. As anticipated [21], the action of diazomethane resulted in preferential migration of the unsubstituted methylene group to furnish **18** in 50% overall yield from **15**. The immediate consequence of this selectivity was the possibility of obtaining **19** by subsequent reduction with zinc dust in acetic acid at room temperature. Especially noteworthy are the quantitative nature of this transformation and the capacity for producing reasonable amounts of **19** in excellent overall yield (43%).

The functional group array in **19** lent itself quite satisfactorily to condensation with lithium di-3-butenylcuprate to deliver **20** (76%). The time had now arrived to utilize the second chlorine atom to direct the introduction of a needed double bond (Scheme III). In order to streamline the synthesis, the stereoisomeric chlorohydrins **21** obtained by the addition of methylmagnesium bromide to **20** were ozonolyzed and acetalized in advance of reduction with lithium in liquid ammonia [22]. This series of reactions could be performed without the purification of **22**, thereby permitting substantial throughput of material to **23** (59% from **20**).



Scheme III

From the background experience gained from processing **8**, it seemed opportune to investigate the hydrolysis of **23** and **24** together with the Lewis acid-promoted cyclization of this aldehyde. As before, some ring closure was already observed during the deblocking maneuver. Once again, purposeful installation of the third five-membered ring with $SnCl_4$ and oxidation of the resulting tricyclic