

PART-B

CHAPTER 1

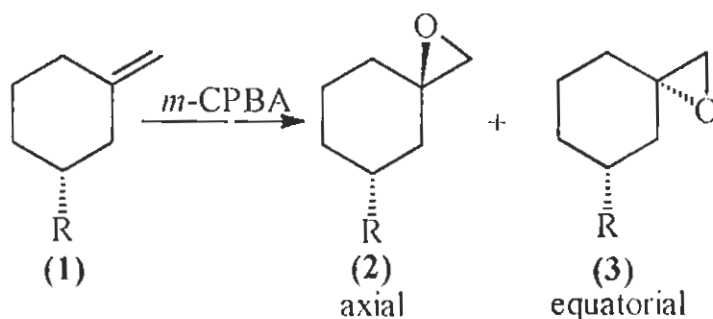
INTRODUCTION

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PART-B

Controlling the trajectory of the approach of a reagent by means of a remote substituent remains an intriguing phenomenon and there have been periodic reports in the literature on this subject.¹⁻⁴

In an attempt to probe the stereoelectronic factors involved in the approach of electrophilic species on methylenecyclohexanes, Johnson⁴ investigated a series of methylenecyclohexanes which were equatorially substituted at C-3 to minimize the involvement of steric factors on the reaction pathway. The reagents examined were mercuric acetate, osmium tetroxide, and *m*-chloroperbenzoic acid. In each series, it was observed that there was an increase in the proportion of axial attack with the increase in the electronegativity of the 3-equatorial substituent. Epoxidation of the trimethyl silyl analogue 1 ($R = \text{SiMe}_3$) gave a 52:48 ratio of epoxides 2 and 3, respectively (Scheme-1).



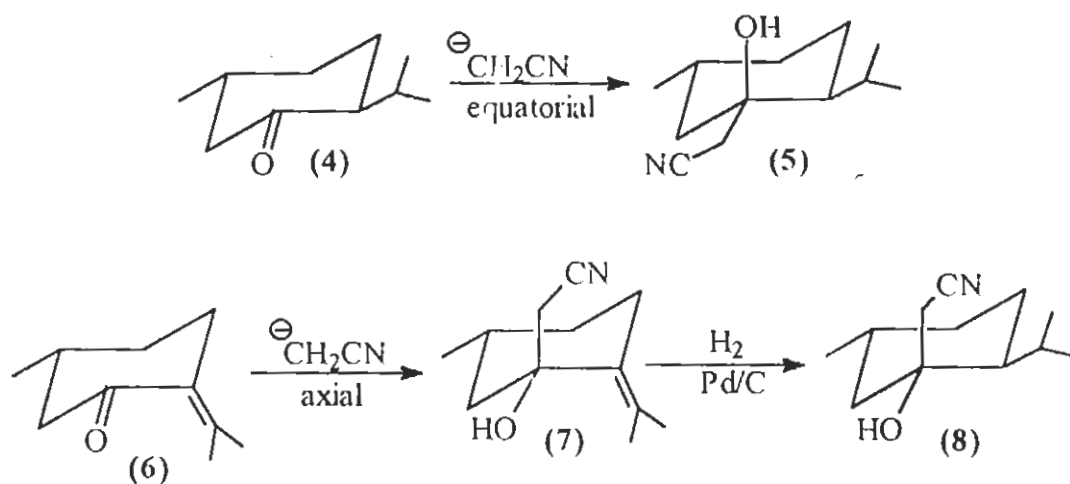
Scheme-1

The phenyl analogue and proton surrogate (4-*t*-butyl derivative) each exhibited ~ 70% of attack from the axial face, whereas the most electronegative substituent, the *p*-

trifluoromethyl phenyl group, provided a 75:25 ratio of epoxides **2** and **3**, respectively. A similar trend in axial selectivity was also observed in the addition reactions of mercuric acetate. These results are consistent with Cieplak⁵ postulate that the stereochemical outcome of reactions on cyclohexanoid systems could be controlled by orbital interactions regardless of the specific reaction mechanism. Cieplak⁵ has stated that the interactions of filled σ orbitals with the developing vacant σ^* orbital along with incipient bond formation imparts stabilization to the transition state in these systems. Therefore, during axial attack the developing σ^* orbital interacts with the filled orbitals of the C2 and C6 carbon-hydrogen bonds of the cyclohexane systems, while during equatorial attack the σ^* interacts with the C2-C3 and C5-C6 ring bonds. Although steric hindrance favors equatorial attack, stereinduction⁶ from hyperconjugative effects favours axial attack since the carbon-hydrogen bonds are better electron donors than carbon-carbon bonds. Furthermore, electron withdrawing substituents decrease the inductive effect of the ring-bonds, and the σ_{CC} stabilization of the transition state which lead to a higher percentage of axial attack.

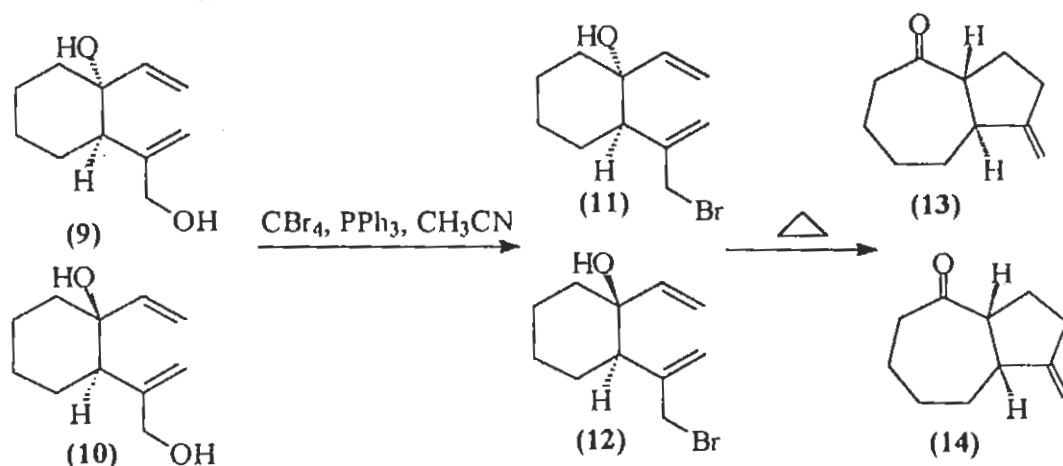
Another contribution to the understanding of axial vs equatorial selectivity in cyclohexane systems has been reported by Trost,^{2,3} who noted a high level of axial selectivity in additions of acetonitrile anions to cyclohexanones and cyclohexenones. An exception to this trend was found in the addition of the acetonitrile anion to menthone **4**, which contains an isopropyl group at C-2, where the predominant direction of attack now come from the sterically less hindered equatorial direction to afford nitrile **5**. Since the incorporation of an acetaldehyde fragment in an axial fashion was required for a future synthetic project, the nature of the C-2 substituent was varied and pulegone **6** was treated with acetonitrile anion to afford adduct **7** (Scheme-2). Catalytic hydrogenation of **7** afforded the nitrile **8**, which was the axial addition isomer of **5**. Therefore, pulegone **6**, which contains an isopropylidene substituent at C-2, can be used as a surrogate to enhance stereoelectronic control of acetonitrile anions. The results of Trost suggest that

the hybridization change in our epoxidation reactions may be the key feature in the observed stereoselectivity. Thus, in enone **6**, which contains α,β -unsaturated carbonyl substituent, the stereoelectronic factors reorder the transition state to provide an axial approach of the electrophilic and nucleophilic reagents, respectively.



Scheme-2

Recently Ko-Chung Lin¹ developed a methodology for the synthesis of hydroazulenoid ring system, which constitutes the carbocyclic framework observed in the guaianolides and pseudoguaianolides. He synthesized *trans* **13** and *cis* **14** hydroazulenones from *cis* **9** and *trans* **10** divinyl substituted diols, respectively, via oxy-Cope rearrangement (Scheme-3).



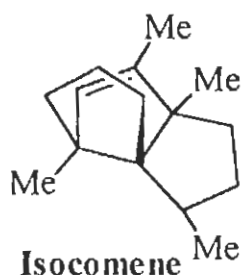
Scheme-3

The isolations of cyclopentanoid natural products are regularly reported in literature. They possess a wide range of biological activities, such as antitumor, cytotoxic, antifungal, antihelminthic, antischistosomal, anti-allergenic and plant growth regulatory properties.⁷ A prevailing trend has been divided these systems into two main structural classes. The first group can be characterized by the presence of tricycloundecane ring system, which is common to a growing list of natural products such as hirsutene, coriolin, isocomene, pentalene, inodhephene, laurene, and retigeranic acid.^{8,9} The second group consists of fused cyclopentanoid natural products. The structural characteristics of this class range from the sesquiterpene skeleton of the guaianolides and pseudoguaianolides, with their 5/7 system,^{7,9} to the recently isolated nonisoprenoids precapnelladiene, dactylol, and poitediol, which contain a 5/8 ring system, as well as the rapidly growing list of sesquiterpene and diterpenoids of the ophiobolins, teleplastins, fusicoccin, and cycloaranosene variety, which share 5/8/5 ring system.

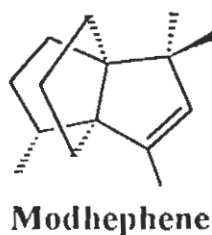
The interesting molecular architecture of these natural products has also continued to challenge organic chemists and several synthetic strategies have now emerged to access

these systems.⁸⁻¹⁰ Although numerous achievements in the synthesis of cyclopentanoid natural products have been reported,⁸⁻¹⁰ most of the approaches have relied upon a stereochemical bias in the ring systems to control substitution patterns.

The first naturally occurring triquinane¹¹ to be synthesized was isocomene¹², a sesquiterpene hydrocarbon isolated from several plant sources, which contains an angular 5,5,5-ring fusion. The general approach to these angular polycyclopentanoids has been to exploit the stereochemistry bias inherent in the *cis*-fusion of 5,5-ring systems that limits the approach of reagents to attack from the less hindered convex face⁸. This bias has also been used to facilitate stereochemical control in other tricycloundecane structures such as coridine, which has exhibited potent antitumor activity and contains a highly functionalized, linear 5,5,5-ring fusion.

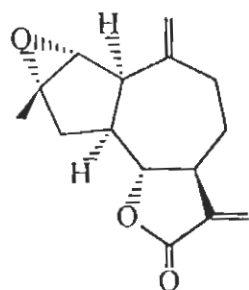


Another class of the triquinane group of natural products is represented by modhephene, which contains the theoretically interesting propellane architecture of three cyclopentane rings.

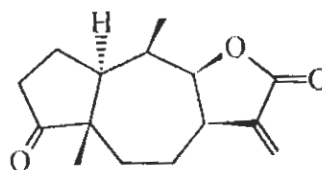


Whereas the incorporation of a number of quaternary carbon was the principle challenge in polyquinanes, the control of ring junction stereochemistry as well as relating remote centers of stereochemistry become additional challenges when cyclopentanoid structures are fused on alternate ring systems. The guaianolide and pseudoguaianolide groups are representative of a general class of sesquiterpene lactones^{9,13} which share the hydroazulene skeleton.

Estafiatin, a constituent of the useful medicinal herb *Artemisia mexicana*, contains the thermodynamically less stable *cis*-7,5 ring junction and belongs to the guaianolide class of lactones, while confertin represents the related group of pseudoguaianolide lactones which share a *trans* ring-fusion. Bakkenolide 'A' and Ceroplasteric acid exemplify the enormous variety of structural characteristics that can be found in cyclopentanoid natural products.

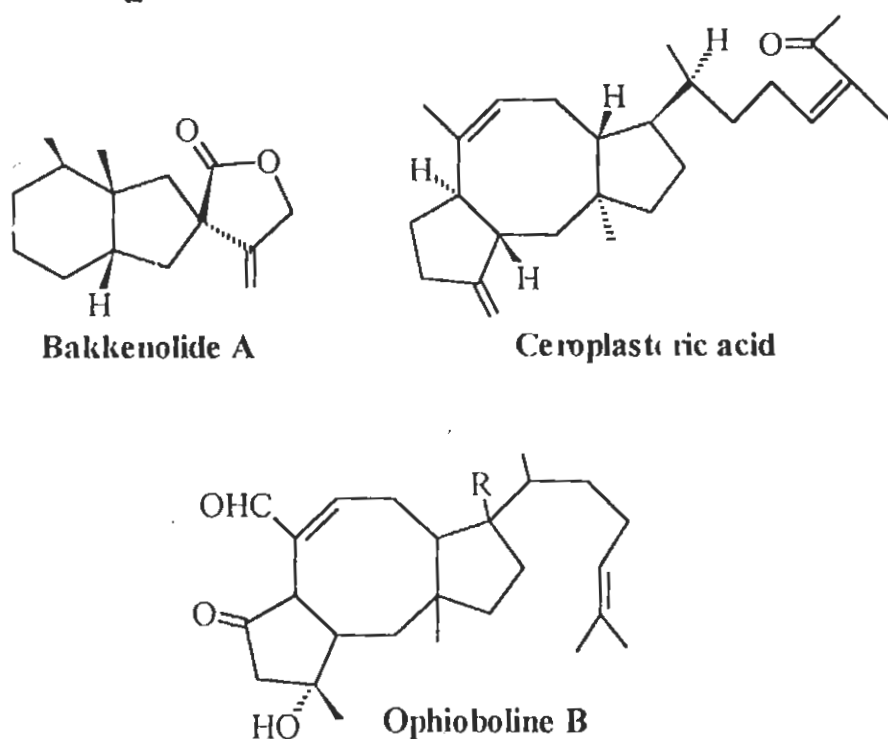


Estafiatin

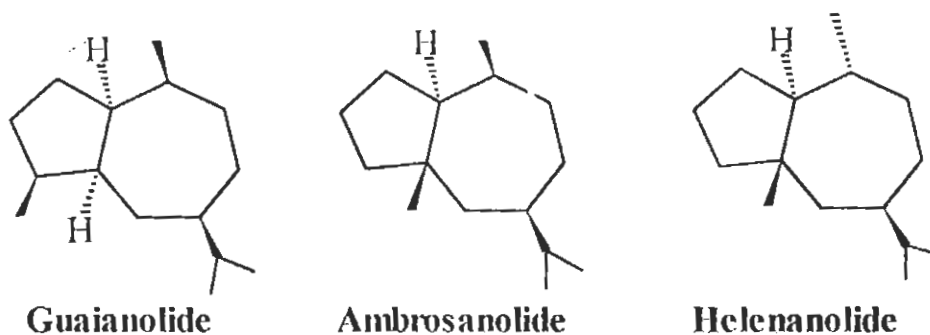


Confertin

Bakkenolide A^{9,14} belongs to the eromophilane class of sesquiterpenes, which are isolated from *Petasites Japonicus*, and contains an hydroindane ring fusion combined with a structurally novel β -methylene- γ -lactone moiety. The sesquiterpenoid ophiobolin and cereplastol groups¹⁵ are isolated from fungi and insects, respectively, and combine numerous stereogenic centers on a tricyclic 5,8,5-ring system, which is illustrated by ceroplasteric acid.



The guaianolide and pseudoguaianolide groups of natural products comprise one third of all known sesquiterpene lactones^{9,13} and many members of this group exhibit a wide range of biological activities which has been attributed to the highly reactive α -methylene lactone moiety.⁷ A survey of activities in this area reveals only modest success with the majority of synthetic strategies being aimed at the pseudoguaianolides, a discrepancy that can be attributed in part to the difference in location of single methyl substituent. In the pseudoguaianolides, classified as ambrosanolides and helenanolides, this methyl group is strategically located at the ring junction, which allows for stereochemical as well as regiochemical control of substitution patterns on the cycloheptyl ring. However, in the guaianolides this methyl substituent is located on the cycloheptyl ring which offers no protection against epimerization of the thermodynamically less stable 7,5-ring fusion, and provides no means to relate remote centers of stereochemistry.



In the present work experiments are conducted on compounds of the type (A) and (B) illustrated below. The effects of solvents as well as trajectory of attack of different electrophilic reagents are explored. Based on the results of the cyclohexane systems, different cyclic systems have been evaluated. This study would prove to be very valuable in determining the scope and limitations of control of diastereoselectivity by remote substituents on cyclic systems.

