π- FACIAL SELECTIVITIES DURING NUCLEOPHILIC AND ELECTROPHILIC ADDITIONS TO 7-NORBORNYL AND RELATED SYSTEMS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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To

My Father

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India - 500 134, under the supervision of **Professor GOVERDHAN MEHTA.**

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of the other investigators.

FAIZ AHMED KHAN

CERTIFICATE

Certified that the work embodied in this thesis entitled: **"π-Facial Selectivities During Nucleophilic and Electrophilic Additions to 7-Norbornyl and Related Systems"** has been carried out by Mr. **FAIZ AHMED KHAN** under my supervision and the same has not been submitted elsewhere for a Degree.

GOVERDHAN MEHTA
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

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ABBREVIATIONS

aq.	:	aqueous
Ac_2O	:	acetic anhydride
Bu	:	butyl
DCM	:	dichloromethane
dil.	:	dilute
DAM	:	diazomethane
DIBAL-H	:	diisobutylaluminium hydride
DMAP	:	dimetylaminopyridine
DME	:	dimethoxyethane
DMSO	:	dimethylsulfoxide
Et	:	ethyl
EtOH	:	ethanol
EtOAc	:	ethyl acetate
liq.	:	liquid
mCPBA	:	meta-chloroperbenzoic acid
Me	:	methyl
MeOH	:	methanol
$NaBH_4$	:	sodium borohydride
NBS	:	N-bromosuccinimide
Pr	:	propyl
r.t.	:	room temperature
TBDMSCl	:	t-butyldimethylsilylchloride
TCE	:	tetrachloroethylene
THF	:	tetrahydrofuran
tlc	:	thin layer chromatography
TsCl	:	p-toluenesulfonylchloride

PREFACE

Stereochemical control through generation of stereogenic carbon centers, particularly during additions to trigonal carbon centers, is one of the central themes in organic chemistry. The factors which can profoundly influence the 'face selectivity' during additions to planar carbon center are: steric effects, conformations of the flanking groups, complexation of reagents, product stability, electrostatic factors and stereoelectronic effects. A greater insight concerning the role of each one of these factors is necessary in order to carry out stereochemical transformations in a predictable manner, which is a highly desirable goal for both theoretical and experimental chemists. Recent years have witnessed a great deal of interest among contemporary chemists in understanding the origin of the π-facial selectivities.

Cram in 1952 pointed out the role of steric and conformational factors during nucleophilic additions to cyclic ketones. Since then various factors controlling nucleophilic and electrophilic additions have been extensively explored, as a result of which several models for stereoselection have been proposed by different groups. The important ones in the chronological order are by Dauben (1956), Karabatsos (1966), Klein (1973), Fukui (1976), Felkin-Anh (1977), Ashby (1977), Hudec (1981), Cieplak (1981) and Houk & Paddon-Row (1991). Of these, the two models that essentially focus on the electronic control of

π-face selectivity and which have come under intense critical scrutiny with much ongoing debate in the past few years have been proposed by Cieplak (1981) and Houk & Paddon-Row (1991). The former takes into account the hyperconjugative transition state stabilization by the antiperiplanar σ-bonds into σ^{*} orbital of incipient bond as the determining factor whereas the later emphasizes the role of electrostatic effect in controlling the face selectivity.

The assessment of various factors governing the π-facial selectivities largely depends on the choices of substrates, the π-faces of which are equivalent, as much as possible, with respect to each of the other effects. Cyclohexane based systems have been generally exploited for this purpose and the same set of experimental data has been used to evaluate various models described above, despite the intrinsic flaw that the two π-faces of the trigonal center in these e.g. cyclohexanone and methylene cyclohexane systems are sterically non-equivalent (axial vs equatorial approach. Thus, there isaneed to devise sterically neutral systems that can serve as incisive probes for segregating steric vs electronic effects in π-face selection.

Our search for such a system led us to the endo substituted 7-norbornanone and 7-methylenenorbornane derivatives which appeared ideally suited for studying face-selectivities, in sterically neutral situations, through long-range electronic perturbations. The 7-Norbornyl system attracted our attention on account of the following structural

features: a) the C_7 sp_2 carbon in these systems is elevated above the $C_2C_3C_5C_6$ plane while the endo-substituent lie below this plane, i.e., on the blind side of the approach to the C_7 center. b) the endo R group can be electronically fine-tuned without perturbing the steric environment around C_7 and c) the conformational rigidity and well documented reactivity pattern of 7-norbornyl system was an additional advantage in obtaining unambiguous results.

The present thesis entitled "π-facial selectivities during Nucleophlilic and Electrophilic Additions to 7-Norbornyl and Related systems" recounts our efforts directed towards the evaluation and understanding of some of the fundamental issues concerning the origin of π-facial diastereoselection in endo-substituted norbornyl and related systems. Our initial investment of efforts to successfully segregate the steric and electronic factors were amplified to further discriminate the constituent elements of electronic component during additions. Attempt was also made to gauge the role of ground state geometric distortions in controlling the 'reagent traffic' in norbornyl systems. The thesis has been arranged under six main sections, titled, I. Introduction, II. Results and Discussions, III. Summary, IV. Experimental, V. Spectra and VI. References.

In the first section, a brief but up-to-date account of important experimental and theoretical work, relevant to the ongoing debate on the origin of π-facial selectivities along

with few popular models of stereoselection including those which are the subject of intense debate and scrutiny in recent years, are provided.

The second section, which is further divided into two subsections, gives an account of synthetic procedures leading to numerous derivatives of norbornyl and related systems, nucleophilic and electrophilic additions to these systems,stereochemical analyses of the addition products by unambiguous methods and attempts to interpret the experimental results in the light of various models and theories of stereoselection.

The subsection A narrates the results of nucleophilic additions to endo-mono- and endo, endo-disubstituted 7-norbornanones, 7-norbornenones and bicyclo[2.2.2]octanones employing metal hydrides (e.g., $NaBH_4$, $LiAlH_4$, $Li(t\text{-}OBu)_3AlH$ and DIBAL-H) and alkyllithium (e.g., CH_3Li). The results described convincingly demonstrate the profound influence of the remote endo-substituents in controlling π-facial diastereoselection during nucleophilic additions. Disubstituted endo-7-norbornenones have been exploited to explore the role of ground state geometric distortions anticipated for these systems. Extension of our studies to endo, endo,-disubstituted bicyclo[2.2.2]octanones was undertaken to make our observations more general. The two possible regioisomers of endo-monosubstituted bicyclo[2.2.2]octanones provided an opportunity to segregate and evaluate the two components of the electronic effect viz, electrostatic and

orbital interactions. Regiochemistry of the products during one-carbon ring expansion of 7-norbornanones enroute to endo-monosubstituted bicyclo[2.2.2]octanones which provides further support to our views on π-facial diastereoselection is also discussed (Appendix).

The subsection B describes the electrophilic additions to 2,3-endo, endo-disubstituted 7-methylenenorbornane, 2-endo-substituted-7-isopropylidenenorbornanes and 5-endo-substituted 7-isopropylidenenorbornenes. The electrophiles studied include m-CPBA, BH_3, $Hg(OAc)_2$, Br+, $^1O_2$ and CCl_2.

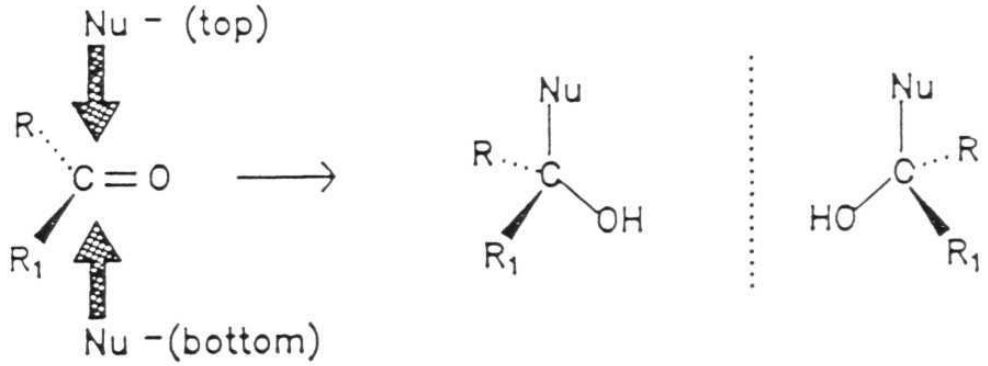
A summary of our experimental results on nucleophilic and electrophilic additions to norbornyl and related systems constitutes section III. The sections IV, V and VI contain details of the experimental procedure, spectra of some of the key compounds and relevant literature citations, respectively.

The results enumerated above constitute an important body of experimental data on the origin of π-facial diastereoselection in view of the conflicting theories and current controversy. Our efforts provide a better understanding of the interplay of various factors such as steric, electronic and electrostatic in determining the origin of π-face selectivities. We hope that these results will stimulate others[70] in designing and studying newer systems to test our mechanistic findings and interpretations.

I. INTRODUCTION

Stereochemical control through generation of stereo-;enic carbon centers is one of the central themes in organic :hemistry. The most common way of generation of stereogenic :arbon centers is through addition of reagents to trigonal :arbon centers to give tetrahedral centers. In principle, :he approach of the achiral reagent during additions to ɔlanar trigonal carbon center is equally likely from either ɔf the two faces (top and bottom), resulting in the formation of racemic mixtures from achiral precursors, Fig.I.

Fig.I



The reaction is known as asymmetric synthesis[1] or asymmetric induction when the two stereoisomers shown in Fig.I are formed in unequal amounts. One of the ways of achieving chiral induction is to have a chiral center in either one or both the ligands (R & R_1) attached to trigonal carbon. This chiral center which is already present in the molecule dictates the predominant approach of the reagent from one of the two faces at the reaction site resulting in the formation of unequal amounts of two stereoisomers, in this case called, the diastereomers. In other words the presence of a

chiral center in the molecule makes the two faces of the planar carbon diastereotopic, resulting in the formation of unequal amounts of diastereomers and is called diastereoselective synthesis.

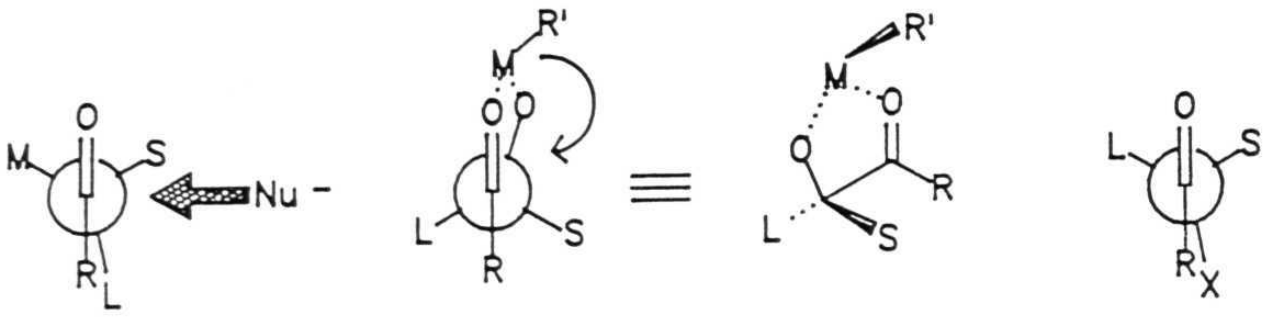
To execute diastereoselective synthesis in a required fashion, a thorough knowledge and understanding of the various factors governing the face selection during additions to trigonal carbon centers is a highly desirable goal. Several factors can influence the face selectivity. The most important factors which were discovered as early as 1952 by Cram[2] are steric and conformational effects. The role of these factors in determining the face selectivity is fairly well understood and few empirical rules have been proposed, depending on the substrates, which predicts qualitatively the predominant approach of the reagent based on the conformation of the chiral center already existing in the molecule. Other factors which also play a crucial role but in a more subtle way in determining the face selection are: torsional strain, complexation of reagents, product stability, electrostatic factors and stereoelectronic effects. A greater insight concerning the role of each one of these factors is necessary in order to carry out stereochemical transformations in a predictable manner. Recent years have witnessed a great deal of interest among contemporary chemists in understanding the origin of the π-facial selectivities.[3-18]

Models of Stereoselection:

Cram[2] in 1952 recognized the role of steric and conformational factors during nucleophilic additions to acyclic ketones. Since then various factors controlling nucleophilic and electrophilic additions to trigonal carbon centers have been extensively explored, as a result of which several models for stereoselection have been proposed by different groups. The important ones are discussed below:

Cram's Model[2]:

Cram was the first chemist to propose an empirical rule of "steric control of asymmetric induction" to predict qualitatively the formation of predominant isomer during nucleophilic additions with organometallic or metal hydride reagents to acyclic ketones possessing an adjacent chiral center. The rule states that when the asymmetric carbon C^* in the ketone $RCOC^*$ SML (where S, M & L stand for small, medium and large groups attached to C^*) is so oriented that the carbonyl function is flanked by two smaller groups (S & M) attached to C^*, the reagent (R^- or H^-) preferentially approaches the carbonyl group from the side of the smallest group S.[4] Cram's rule, summarized in 1, assumes a transition state conformation in which the carbonyl oxygen is anti-periplanar to the largest group (L) attached to the neighbouring chiral carbon. The rule applies only to reactions that are kinetically controlled and not to the thermodynamically controlled processes where subsequent equilibration produces more stable product predominantly. The



1 2 3

stereochemical outcome of addition to ketones having groups such as OH, NH_2 or OMe on the α-chiral center is predicted by Cram's rule[5] based on a rigid cyclic model as shown in 2. Approach from the side of the small group is again favored. Failure of model 2 to predict correctly the resultant major diastereomer in addition to ketones having a polar substituent, such as halogen, on the α-chiral carbon led Cram to propose[6] the dipolar model 3. The dipoles of the carbonyl bond and the C-X bond oppose each other and to minimize this they are placed anti as shown in 3. Karabatsos[7] modified Cram's rule and proposed modifications in the transition state conformation of the ketone based on the assumption that the transition state is characterized by little bond making and breaking and hence the arrangement of the three groups of the asymmetric carbon atom with respect to the carbonyl is the same as in aldehydes or ketones, i.e. one group eclipsing the carbonyl as shown in Fig.II. Product

Fig.II

specificity in all the models described above therefore depends on the relative magnitudes of Nu^- vs S and Nu^- vs M steric interactions.

Dauben's Model:[8,18]

Dauben[8] was the first chemist to rationalize the stereochemistry of the metal hydride reduction of substituted cyclohexanones. During the reduction of 4-tert-butylcyclohexanone with lithium aluminium hydride, the nucleophile approaches predominantly (90%) from the more hindered axial face to produce more stable equatorial alcohol. The more hindered ketone 3,3,5-trimethylcyclohexanone is attacked predominantly (55 to 75%) from the less hindered equatorial side. To explain these results Dauben suggested the concept of "product development control" and "steric approach control". He suggested the formation of an initial complex and the transfer of the hydride in the complex results in rehybridization of the carbonyl carbon atom from sp^2 to sp^3. A late transition state in which hybridization is largely sp^3 allows the relative stabilities of the products to be reflected in the transition state. In the case of an unhindered ketone such as 4-tert-butylcyclohexanone, Dauben suggested that the developing sp^3 hybridization is the controlling factor, hence that "product development control" is observed. On the other hand C_3 axial methyl group of 3,3,5-trimethylcyclohexanone hinders the nucleophile in its axial approach, decreasing the ease of formation of this complex. This results in the favoring

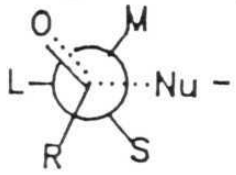
of equatorial attack, and "steric approach control" determines the stereochemistry of reduction. These and other results have been generalized, leading to the conclusion that reduction of unhindered ketones is governed by product development control and that reduction of hindered ketones is governed by steric approach control. The product development control would require a late transition state resembling the products, whereas steric approach control would require an early transition state resembling the reactants.

Felkin-Anh Model:[9,10]

In 1968 Felkin[9] proposed a model based on the concept of torsional strain which was subsequently supported by Anh and Eisenstein's (1977) ab initio theoretical calculations.[10] The model generally known as Felkin-Anh model, has been widely accepted and has played a significant role in understanding the stereoselectivities of variety of reactions.

Felkin's model[9a] for the interpretation of the steric outcome of nucleophilic reactions encompassing both open-chain carbonyl compounds and cyclohexanones, was based on the following four premises: (a) The transition state in the hydride reductions are, in all cases, essentially "reactant like", rather than "product like" as suggested by Dauben for unhindered cyclohexanones. (b) Torsional strain (Pitzer strain) involving partial bonds and fully formed bonds in transition states represents substantial fraction of the

strain. (c) Important steric interactions involve Nu^- and R rather than the carbonyl oxygen as assumed by Cram and Karabatsos. On this basis, the least strained of the six possible staggered conformations is 4, followed by 5 and 6 (the other three all involve gauche interactions between Nu^- and L, and at the same time between R and M or L). (d) Polar effects stabilize those transitions states in which the separation between Nu^- and an electronegative group (L, M or S) is greatest, and destabilize the others.



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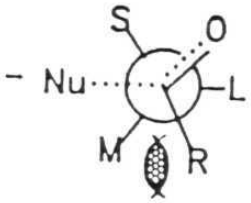

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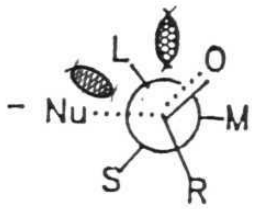

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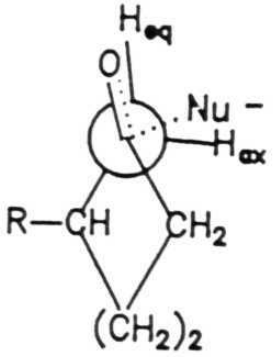
In the case of cyclohexanones[9b] both torsional and steric strain cannot be minimized simultaneously as in the case of acyclic substrate model 4. Felkin pointed out that in the reactions of cyclohexanones formation of the axial alcohol (equatorial attack) implies a partial eclipsed transition state 7 involving some degree of torsional strain, and formation of equatorial alcohol (axial attack) implies an essentially staggered transition state 8 involving some degree of steric strain. He therefore, suggested that in the absence of polar effects their stereochemical outcome is determined by the relative magnitude of torsional strain in 7 and of steric strain in 8.

The predominant formation of the equatorial alcohol in unhindered cyclohexanones is due to torsional strain in the



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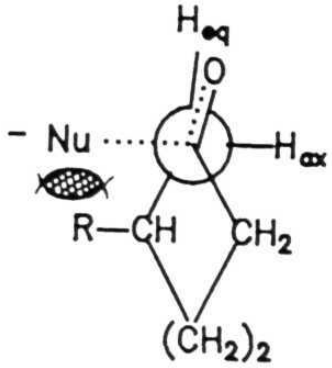
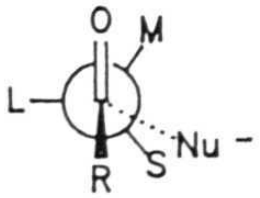


8

reactant-like transition state 7, and not the kind of steric strain in "product development control" model proposed by Dauben. Making R bulky will lead to the increased steric strain in transition state 8 resulting in the predominant formation of axial alcohol via transition state 7.

Anh and Eisenstein[10] supported the model proposed by Felkin and suggested that the Felkin's hypothesis may be advantageously replaced by the assumption of non-perpendicular attack as shown in 9 and 10. Obviously the steric hindrance encountered by the nucleophile is much more in 10 than in 9. This model also accounts for the experimentally observed fact that the asymmetric induction is enhanced as the size of the R group is gradually increased. Since as R becomes increasingly bulkier, the incoming nucleophile is pushed further and further towards the neighboring chiral carbon and can "feel" better the difference between S (in 9) and M (in 10), which should lead to increased selectivity.



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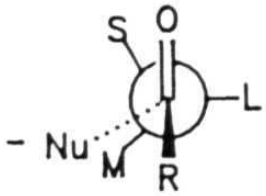
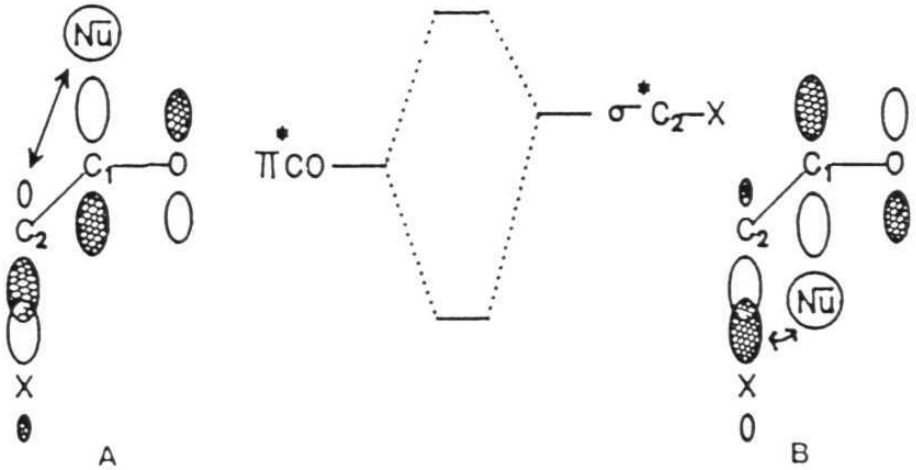


10

Anh further proposed the anti-periplanar effect and the ring flattening rule based on Frontier molecular orbital considerations. The HOMO of nucleophile interacts with the LUMO of substrate (carbonyl compounds) during nucleophilic addition. Therefore, the most reactive conformation of the substrate is that with lowest LUMO. This corresponds to the geometry in which C_2-X bond is parallel to the π system, as there is then a good overlap between the π^*CO orbital and the low lying σ^*C_2-X orbital, leading to a stabilization of the LUMO, Fig.III. The nucleophile may now approach the conformer corresponding to the lowest LUMO either from the anti-periplanar or syn-periplanar direction with respect to C_2-X bond as shown in Fig.III. The latter is disfavored for

Fig.III



two reasons (i) while the anti-attack with respect to X leads to an in-phase overlap between Nu^- and σ^*C_2-X (Fig.III A), syn-attack leads to an out-of plase overlap between Nu^- and σ^*C_2-X (Fig.III B); (ii) syn-attack implies an eclipsing of C_1-Nu^- and C_2-X bonds (Fig.III B).

In cyclohexanone systems the anti-periplanar effect suggests another factor which can govern the selectivity. It is clear that if the ring may be flattened, as indicated in Fig.IV, axial attack may approach anti-periplanarity to the C_2-H_{ax} and C_6-H_{ax} bonds. Equatorial attack cannot approach anti-periplanarity to the C_2-C_3 and C_5-C_6 bonds. The more flattened the ring, the more axial attack ("flattening rule").

Fig.IV

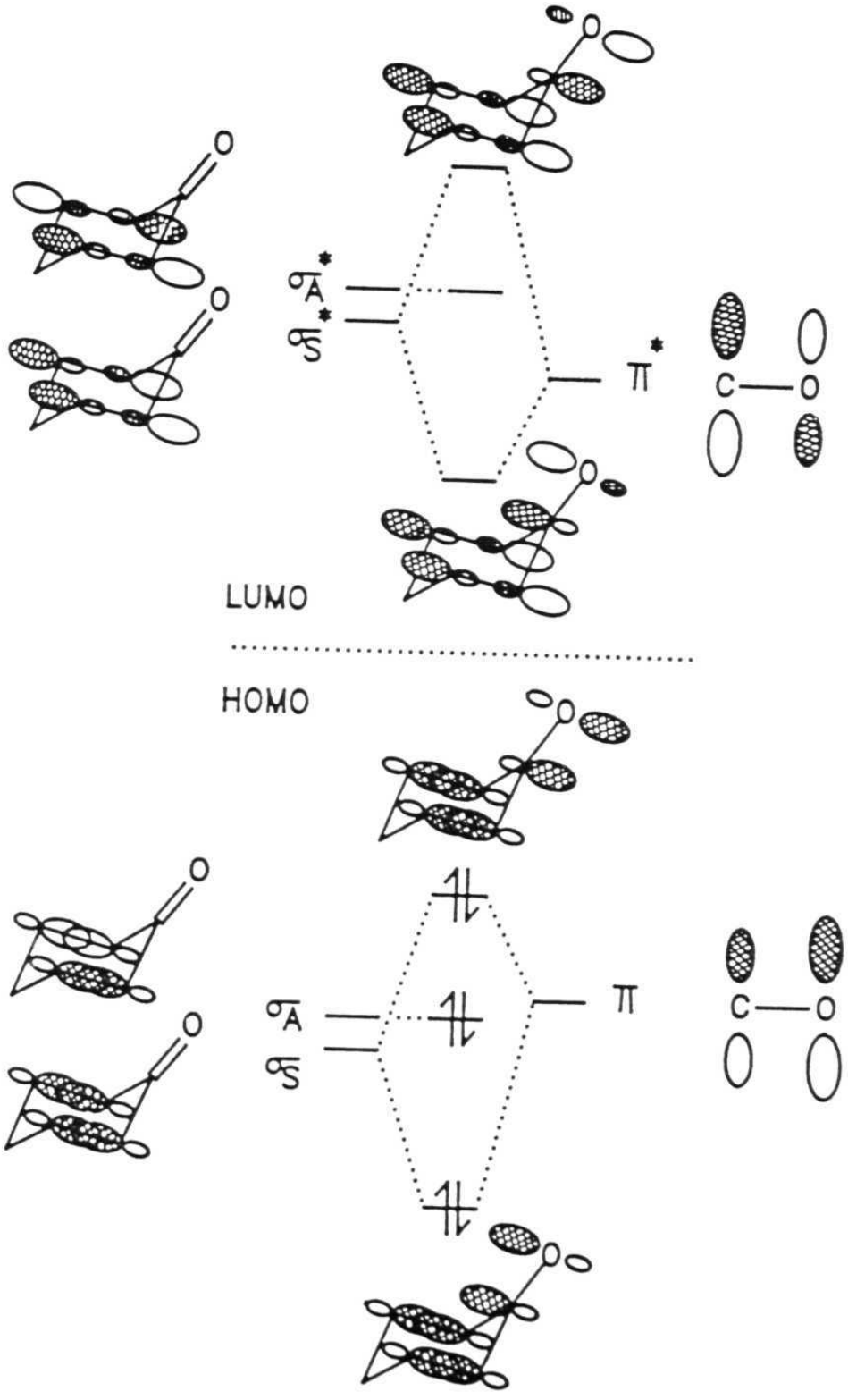
The Felkin-Anh model basically predicts the same stereochemistry as Cram's but provides a more quantitative assessment of 1,2-asymmetric induction.

Klein's Model:[11]

Klein[11] was one of the first chemist to conceive and propose a model based on electronic effects in the reactions of cyclohexanones. He suggested that the β C-C bonds enter into a hyperconjugation interaction with π electrons of the carbonyl (or exocyclic double bond). The symmetrical σ and σ^* orbitals interacts with π and π^* orbitals respectively forming two orbitals of different energy in each case, as shown in the Fig.V. LUMO of the carbonyl which participates during nucleophilic attack, is lowered in energy by inter-

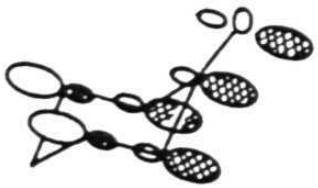
action with β C-C bonds and has larger lobes on the side of the β C-C bond. This unsymmetrical extension of π^* lobes

Fig.V



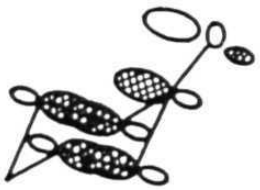
facilitates attack from the axial face from which better interaction with the incoming nucleophile is possible in the absence of steric effects. Similarly the bonding orbital of highest energy (HOMO) will have the larger electron density of the π system on the face opposite to β C-C bonds due to anti-bonding interactions between the carbonyl (or exocyclic double bond) and the orbitals of C-C bonds. Electrophilic attack on the exocyclic double bond of methylene cyclohexanes which involves the HOMO of π-system is therefore predicted to take place predominantly from the equatorial face.

Alternatively, interactions between the occupied and the corresponding vacant orbitals as shown in 11 and 12 may be considered to explain the same problem. This interaction leads to different electron density on the two faces of the



π orbital

11



π^* orbital

12

plane containing the trigonal atom. Electrophilic attack involves preferential equatorial approach by interaction with π orbital 11, but nucleophilic attack involves preferential axial approach by interaction with π^* orbital 12.

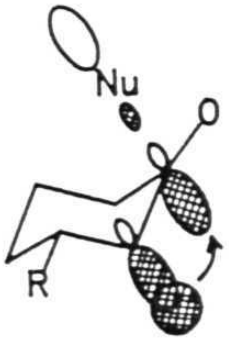
Hudec's Model:[12]

Hudec[12] in his "twist angle theory" using semiempirical MO calculation showed that the π^* orbital of the carbonyl carbon of asymmetric ketones deviate from orthogonality. This small deviation, measured by twist angle, of the p orbital of carbon atom from the normal position perpendicular to the carbonyl plane takes place to effect greater overlap with a vicinal σ bond. The magnitude of twist angle may be used to predict the configuration of the diastereomeric alcohols formed during the metal hydride reduction of ketones. It was also proposed that a nucleophile approaches a carbonyl group preferentially from the side of obtuse angle with respect to O-C bond.

Cieplak Model[13]**:**

The model proposed by Cieplak[13,14] is in a sense just reverse of the Anh's model in which the transition state stabilization by delocalization of the newly formed C-Nu bond into anti-periplanar σ^* orbital was proposed. Cieplak assumed that the stabilization of the transition state can occur by the delocalization of electrons from anti-periplanar σ bonds into the σ^* orbital, a low-lying vacant orbital, of the incipient bond between the nucleophile and the carbonyl carbon. Thus, the preferred approach of a nucleophile to the carbonyl is from the face anti to the most electron rich allylic σ bonds. The second assumption in this model is that the electron donating abilities of some common bonds are in the order: C-S > C-H > C-C > C-N >

C-O. The stereochemical outcome of the metal hydride reduction of substituted cyclohexanones is therefore governed by which of the vicinal bonds is more electron donating, the C_2-H_{ax} and C_6-H_{ax} or the C_2-C_3 and C_5-C_6 σ bonds. Axial approach is stabilized by electron donation into σ^* orbital of incipient C-Nu bond from anti-periplanar σ C-H bonds, 13 whereas equatorial approach is stabilized by similar electron donation by σ C-C bonds, 14. Since C-H σ bonds are



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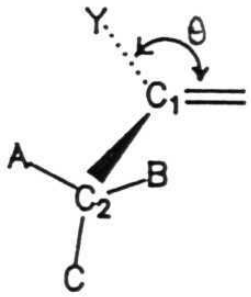
14

postulated to be better electron donors than σ C-C, axial transition state leading to equatorial alcohol is favored over the other. An electron withdrawing group at C_3 makes C_2-C_3 σ bond relatively electron poor and hence disfavor the equatorial transition state 14 resulting in the enhancement of the axial attack.

Houk & Paddon-Row Model:[15-17]

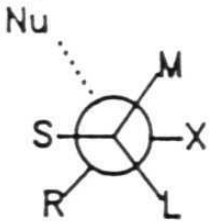
Houk[15,16] and Paddon-Row[17] investigated transition state energetics and performed conformational analysis of the transition structures using ab initio and force-field methods. In their studies particular attention was focused on the angle of reagent attack θ, the rotational preferences of C_1-C_2 bonds and preferred locations of allylic substi-



tuents A, B and C in the transition structures. Calculations on several transition states for nucleophilic additions led them to propose that the charged nucleophiles approach trigonal center with obtuse attack angle θ, of 115° to 130°C. The attack angle θ decreases for additions of organolithium or metal hydride reagents which proceed via four-center transition structures. Theoretical studies of hydroboration and carbene cycloadditions revealed that, for electrophilic attack on multiple bonds, an acute angle of approach is favored.

The calculations performed to assess the conformational preference of methyl group attached to the trigonal center reveal that the allylic C-H bonds prefer a staggered arrangement with respect to partially formed bond during nucleophilic additions. This conclusion, which was originally reached empirically by Felkin[9] and later computationally supported by Anh,[10] was further extended to accommodate all types of additions. The preferred arrangement of the substituents on the α-chiral carbon, which differ in size but possessing similar electronic character, were determined by ab initio or force field calculations. For nucleophilic additions with large θ (15), the conformational preference

is such that the largest group (L) is anti to the attacking nucleophile, the medium sized group (M) is inside (near the double bond), and the smaller group (S) is outside (away from the double bond) in the crowded region between R and approaching nucleophile. This "outside crowded" model is similar to Felkin-Anh model and predicts the same major product as is predicted by Cram's rule. By contrast, in an "inside-crowded" model, the preferred location of substituents is as follows: L, anti; M, outside; S, inside. Model calculations suggest that hydroboration follow such an "inside-crowded" model for chiral centers on either carbon (16) or boron (17). Thus, the resulting stereochemistry is



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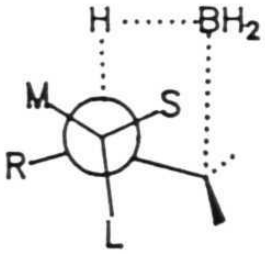

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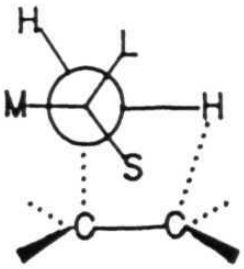

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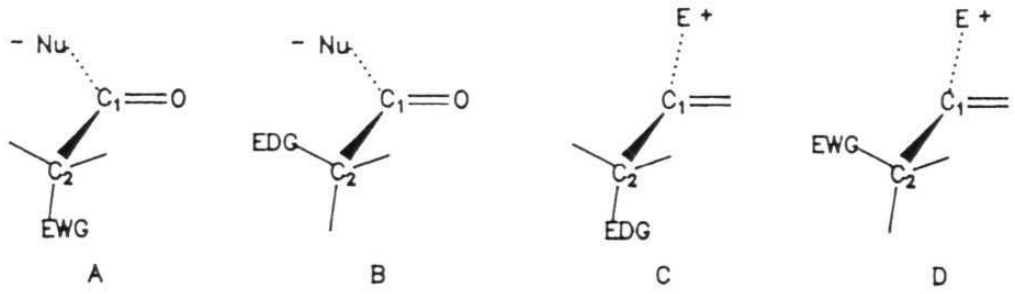
referred to as "anti-Cram" because it is opposite to the stereochemistry predicted by Cram's (Felkin-Anh) rule for nucleophilic additions.

When allylic substituents are either electron withdrawing or donating relative to hydrogen, electronic effects cause these substituents to possess a specific orientation with respect to the attacking reagent. Ab initio calculations indicated that, for nucleophilic attack, electron withdrawing (EWG) allylic group prefer the anti-conformation as shown in Fig.VIA; while electron donating group (EDG)

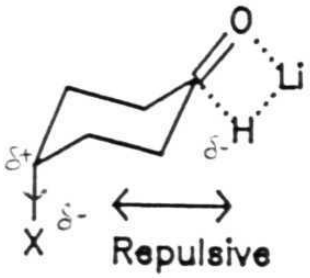
disfavor the anti-position and takes outside (or inside) orientation as shown in Fig.VIB. On the other hand, opposite preferences of donor (EDG) and acceptor (EWG) groups, as shown in Fig.VIC and D, were revealed for electrophilic reactions.

Fig.VI



These results are in sharp contrast to the proposal made by Cieplak[13] in which the donor group always prefers anti conformation with respect to newly forming bond. Thus, Houk-Paddon Row model fully supports Felkin-Anh model and contradicts Cieplak's model. Further, recent calculations on model systems by Houk et.al.[16] suggests the importance of electrostatic interactions between remote polar substituents and the incoming nucleophile in determining the face selectivity and claims that the combination of torsional and electrostatic effects rationalize the large body of observed stereoselectivities.[16] The face selectivity found in cyclohexanones is explained by electrostatic or dipole effects of remote polar substituent as shown in 18, 19 and 20.

The electrostatic repulsive interaction between the substituent and the nucleophile destabilize the equatorial attack as shown in 18 and the axial is favored by the



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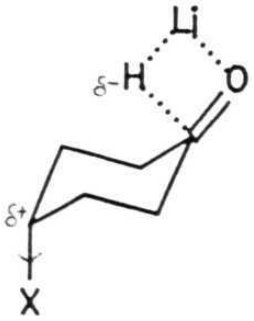

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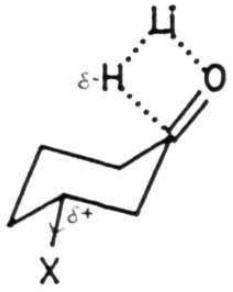


20

attractive interaction between the positive charge at C_4 (19) and the nucleophile. In the case of 3-substituted cyclohexanones 20 an electron-withdrawing substituent induces positive charge at C_3, which stabilizes a negatively charged nucleophile upon axial attack as shown in 20. In the absence of polar substituents, nucleophilic addition occur in such a fashion as to minimize eclipsing strain (Felkin-Anh model). Steric effects can also be influential.

Evaluation of models vis-a-vis experimental data:

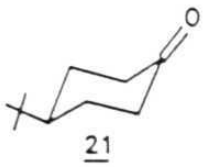
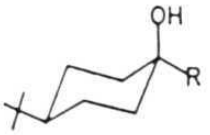
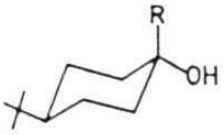
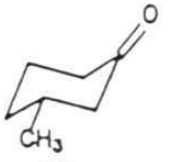
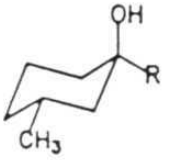
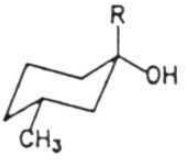
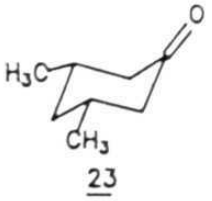
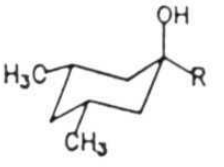
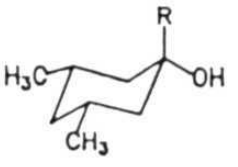
After having discussed various models of stereoselection proposed by different groups (vide supra), we now focus briefly on the important experimental data reported in the literature. We shall concentrate mainly on cyclic systems and focus on the recent ongoing debate on the subject of π-facial diastereoselection.

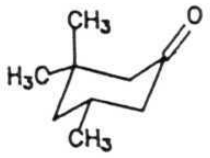
The last two models of stereoselection described above, viz., Cieplak[13,14] and Houk & Paddon-Row[15-17] have come under intense debate and experimental scrutiny during the past few years. Until recently, the same body of experi-

mental data has been used in most cases to explain various models described above. Cyclohexane based systems have been generally exploited for this purpose. Hence, before discussing recent experimental results on some of the other interesting systems, a brief discussion on nucleophilic additions to cyclohexanone will be in order.

Stereoselective reduction of ketones by complex metal hydrides has been investigated by several workers.[18] A large body of experimental data is also available in the literature on nucleophilic additions of organometallic reagents to cyclic ketones.[19] Table 1 lists results of nucleophilic additions of metal hydrides and organometallic reagents to substituted cyclohexanones. 4-tert-Butylcyclohexanone 21 is conformationally locked system with the bulky tert-butyl group in the equatorial position and removed from any steric influence at the reaction center. Metal hydride reductions of 21 takes place predominantly from the sterically more hindered axial face leading to equatorial alcohol as the major product. Addition of organometallic reagents to 21 furnished products derived from predominant equatorial approach. The preference for the equatorial face increases progressively as the size of attacking group is increased from H^- ---> CH^-_3 ---> t-Bu^-, with t-Bu^- giving exclusive equatorial attack. Metal hydride reductions of 3-methylcyclohexanone 22 proceeded with slight enhancement of equatorial attack and organometallic reagents showed greater preference for equatorial approach. An additional

Table 1:

Reagent	Ketone	Solvent	Axial alcohol	Equatorial alcohol	Ref.
	 21				
$NaBH_4$		Me_2CHOH	13	87	18
$LiAlH_4$		Et_2O	8	92	18
$LiAl(OtBu)_3H$		THF	10	90	18
CH_3Li		Et_2O	65	35	19
CH_3MgBr		THF	69	31	19
$t\text{-}C_4H_9MgBr$		Et_2O	100	0	19
$LiAl[OCEt_3]_3H$		THF	26	74	20
$Li[OCEt_2(t\text{-}Bu)]_3H$		THF	95	5	20
	 22				
$NaBH_4$		Me_2CHOH	14	86	13
$LiAlH_4$		THF	13-15	85-87	13
CH_3Li		Et_2O	66	34	13
C_2H_5MgBr		Et_2O	68	32	19
	 23				
$NaBH_4$		Me_2CHOH	20-22	78-80	13
$LiAlH_4$		THF	16-17	88-84	13



24

$NaBH_4$	Me_2CHOH	52-62	38-48	18
$LiAlH_4$	Et_2O	55-63	37-45	18
$LiAl(OtBu)_3H$	THF	88-96	4-12	18
CH_3Li	Et_2O	100	0	19
CH_3MgI	Et_2O	100	0	19
$t\text{-}C_4H_9MgBr$	Et_2O	100	0	19

equatorial methyl group at C_5 resulted in slight further enhancement in equatorial approach of hydride ion in 3,5-dimethyl cyclohexanone 23. In the case of 3,3,5-trimethyl-cyclohexanone 24, additional methyl group is introduced at C_3 axial position and this severely hinders axial attack on the cyclohexanone ring. Approach of the hydride ion shows a great preference for equatorial face in the reductions of 24. The sensitivity of 24 to steric factors is reflected from the large variation in the face selectivity when a bulkier reducing agent such as $LiAl(OtBu)_3H$ is used. Organometallic reagents furnish products of exclusive equatorial attack upon addition to 24.

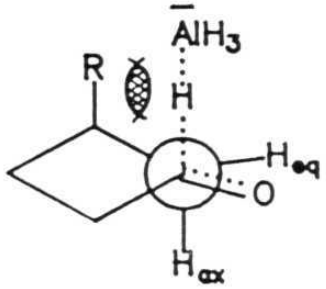
The results described above may be summarized in the following points: (i) smaller groups show axial preference to unhindered ketones; (ii) equatorial preference increases progressively with increasing steric congestion in the

ketone; (iii) unhindered ketones do not respond significantly to the variation in the steric bulk of the reducing agent but hindered ketones show large variation; (iv) larger groups (e.g. CH_3^-, $C_2H_5^-$, i-Pr^-, t-Bu^-, etc.) show equatorial preference in all the ketones with significant enhancement in the case of hindered ones.

Exceedingly large bulk of reducing agent may change or completely reverse the stereochemical outcome of even unhindered ketones such as 21. Very recently Bioreau and coworkers[20] synthesized a highly hindered lithium tris[(3-tert-butyl-3-pentyl) oxy]aluminium hydride and demonstrated highly stereoselective reduction of 21, Table 1. In contrast to other hydrides, reduction of 21 with this hindered reagent proceeds *via* the equatorial attack with high degree of stereoselectivity quite similar to that achieved with sterically hindered trialkylborohydrides.[21]

Felkin-Anh model rationalizes the above results in terms of torsional strain theory and *anti*-periplanarity of the reagent approach. According to this equatorial approach encounters torsional strain between C_2-H_{ax}, C_6-H_{ax} and the incipient bond, whereas the allylic bonds are staggered for the axial approach. In the case of 21, where R=H (see 25), the steric factor is minimal and torsional effect shown in 26 dominates controlling the stereochemical outcome. When R is alkyl as in 24, steric strain gains importance in controlling the stereochemistry. Also it is expected from the transition state models 25 and 26 that an increase in the

steric bulk of the attacking species would destabilize the transition state 25 leading to an equatorial alcohol more than the transition state 26 leading to an axial alcohol, since torsional strain (as in 26) is influenced more by changes in dihedral angle than by changes in steric bulk.



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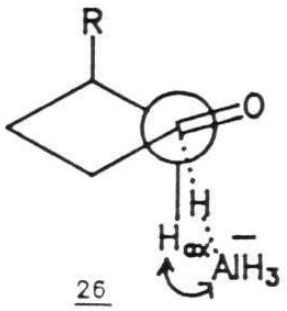


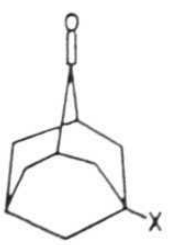
26

Cieplak[13,14] proposed hyperconjugative stabilization of the transition states by anti-periplanar σ bonds into the σ^* orbital of the incipient bond to account for the selectivities found in cyclohexanones. Thus, equatorial transition state is stabilized by electron donation from C_2-C_3 and C_5-C_6 σ bonds whereas axial transition state is stabilized by electron donation from C_2-H_{ax} and C_6-H_{ax} σ bonds. Which pair of σ bonds is better electron donor would decide the stereochemistry of the products. Cieplak argued that C-H bond is better donor than C-C bond and hence axial transition state is favored over equatorial. Consequently, the major product is equatorial alcohol in the reduction of 21. Alkyl substituents on cyclohexanone (e.g., in 22-24) make C_2-C_3 and/or C_5-C_6 electron rich and thus stabilize the equatorial transition state leading to predominant formation of axial alcohol.

Some recent results:

Several new probes have been designed by le Noble, Halterman, Johnson, Houk, Paquette, Vogel among others to study and evaluate the origin of π-face selectivity.

le Noble in his pioneering work[22] used 5-substituted-2-adamantanones as probes for the study of electronic control of π-facial selectivities. 2-Adamantanone may be regarded as made up of two locked chair conformers of cyclohexanone sharing a common keto bridge. The molecule is rigid and the two faces of the trigonal carbon are sterically equivalent. The remote 5-substituent does not alter the steric environment at the reaction site. The response of the approaching reagent to the variation in the 5-substituent should be due to electronic reasons. The important feature of this probe is that it eliminates the equatorial <u>vs</u> axial discrimination, an inherent property of cyclohexanones and both the pairs of allylic bonds crucial for transition state stabilization are C-C σ bonds. This eliminates the controversy about which σ bonds are better donors when the two pairs of bonds are between different atoms (e.g. C_2-C_3, C_5-C_6 and C_2-H_{ax}, C_6-H_{ax} in cyclohexanone systems).



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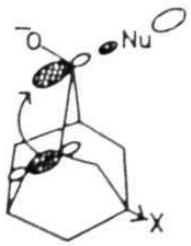

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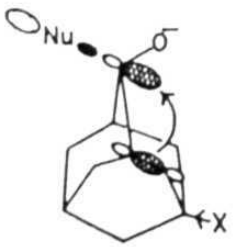
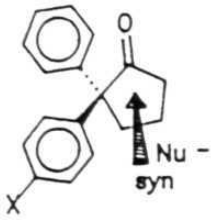


<u>29</u>

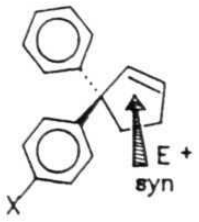
le Noble[22] observed that when X in 27 is electron withdrawing, it directs the approach of the nucleophile from the syn-face whereas the electron donor group X induces opposite selectivity (preferential anti-approach). The selectivities found in all the cases have been generally quite modest e.g. syn : anti ratio of products from $NaBH_4$ reduction and MeLi addition to 5-fluoro-2-adamantanone and 5-trimethylstannyl-2-adamantanone were 58 : 42; 70 : 30 and 43.5 : 56.5; 36.5 : 63.5 respectively. An exceptionally enhanced selectivity was reported in the reduction of 5-substituted adamantanones by substitution of C_5 by positive nitrogen.[23] Furthermore, other types of reactions[24] such as cycloadditions, capture of radicals and cations, oxy-cope rearrangement, etc were employed on adamantyl probe and modest but consistent face-selectivity as a function of C_5 substituent was observed. These results have been mainly interpreted in terms of the Cieplak model, as shown in 28 and 29 for electron withdrawing and donating substituents, respectively.

Halterman[25] in a recent study employed sterically unbiased diaryl substituted cyclopentane systems 30-32. By making one of the aryl ring electron rich or poor by varying the para substituent in that ring, he demonstrated the electronic origin of the face selectivity in these systems. The results obtained from $NaBH_4$ reduction of 30, osmium catalyzed cis-dihydroxylation of 31 and dimethylacetylene dicarboxylate cyclo addition to 32 demonstrate that in all



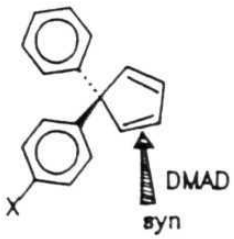
$X=NO_2$, Cl, Br, OCH_3, O,- NH_2

30



$X=NO_2$, Cl, Br, OCH_3, NMe_2

31

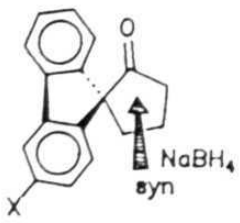


$X=NO_2$, Cl, NMe_2

32

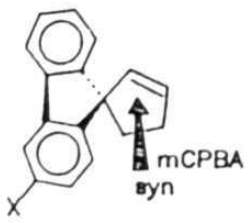
the cases the reagent approaches from the side opposite to more electron rich aromatic ring. The observed selectivities were explained in terms of Cieplak's hyperconjugative model.

Ohwada reported[26] the $NaBH_4$ reduction of sterically neutral spiro[cyclopentane-1,9'-fluoren]-2-one 33 and observed that the anti alcohols (i.e. syn approach of H^- ion with respect to substituent X) were favored in all cases. In the epoxidation of substituted spiro[cyclopent-2-ene-1,9'-fluorenes] 34 the syn epoxides (i.e. syn approach of the reagent with respect to substituent X) were favored in every case. The observed selectivities in these systems were interpreted in terms of orbital perturbations arising from interactions of the π orbitals of the aromatic and the



$X=NO_2$, F, OCH_3

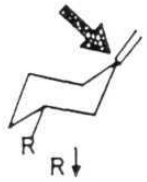
33

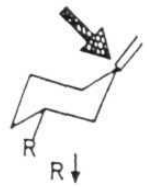


$X=NO_2$, F, OCH_3

34

Table 2:[14]

	CH_3Li ether -78°C	Li_2Me_3Cu ether -78°C	$PhSCH_2Li$ THF -78°C	$PhS(O)(NMe)CH_2Li$ THF -78°C
$Si(CH_3)_3$	15	2	10	55
t-Bu	19	3	11	56
H	21	6	20	--
C_6H_4-OMe-p	24	8	16	66
C_6H_4-Me-p	23	8	19	65
C_6H_6	25	7	15	65
C_6H_4-CF_3-p	28	10	24	72
C_6F_5	34	21	28	70
CF_3	50	42	53	83

	$Hg(OAc)_2$ H_2O 0°C	m-CPBA CH_2Cl_2 0°C	OSO_4/Me_3NO THF/H_2O 25°C
$S(CH_3)_3$	40	52	7
t-Bu	58	60	--
H	70	69	14
C_6H_5	67	70	15
C_6H_4-CF_3-p	70	75	14
CF_3	92	--	--

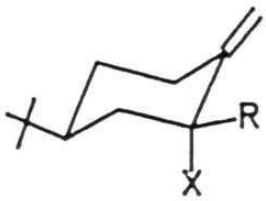
carbonyl moities or of the π orbitals of the aromatic and the olefin moities.

Johnson and coworkers[14] recently carried out an investigation of various reactions of cyclohexanones and methylene cyclohexanes substituted at C_3 by groups of varying electronegativity and of large steric bulk. The reactions examined include organolithium, organocuprate, and sulfur ylide additions to cyclohexanones and oxymercurations, osmylation and per-acid epoxidations of methylenecyclohexanes. Electronegative substitution at C_3 of cyclohexanones and methylene cyclohexanes was found to increase the relative proportion of axial attack in all the cases examined. An increase in the proportion of axial attack was also observed when the electronegativity of a substituent on a carbon nucleophile is increased (Table 2). The authors conclude that their results appear to be inconsistent with the predictions of Felkin-Anh and Klein models of stereochemistry of reactions in cyclohexane based systems, but are consistent with Cieplak model.

Another important contribution to the intriguing debate on the origin of π-facial selectivity was made by Vedejs et al.[27] He studied epoxidations and osmylation of 4-tert-butyl methylene cyclohexane derivatives 35 and 36 to determine if selectivity pattern will reveal σ, σ^* interactions (Cieplak model) within a family of related substrates. The most important finding of this work was that the product ratio is

barely perturbed by the interchange of C_2 axial vs equatorial methyl and methoxy groups (i.e. when R=CH_3 and X=OMe in 35 and 36) and there is no indication of specific σ, σ^*

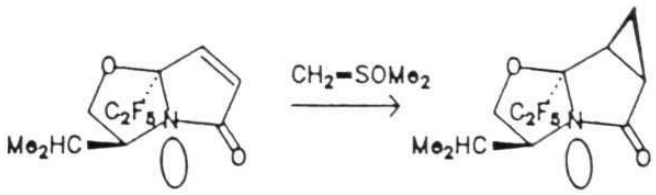
35



36

(Cieplak) effects. The author emphasizes the importance of repulsive terms of the torsional effect (steric repulsions, etc.) in determining face selectivity in these substrates.

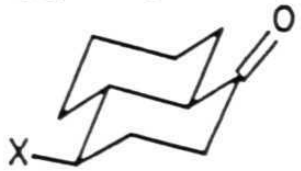
Another serious setback to Cieplak's hyperconjugative model came from the work of Meyers et.al[28] during the cyclopropanation of unsaturated lactam 37 having strong electronegative C_2F_5 group. anti-Cieplak product, 38 predominated the cyclopropanation of 37 by almost 20:1. This was interpreted in terms of electronic perturbation of the π-system of the C=C bond in 37 by the unshared lone pair on the lactam nitrogen.



37 38

Houk and coworkers in their earlier work[15] proposed qualitative rules for the prediction of stereochemistries of organic reactions and also developed semi-empirical computational models to predict the stereoselectivities in nucleophilic additions to carbonyls, electrophilic additions to

olefins and in cycloaddition reactions. In their recent work[16] employing a series of 4-substituted trans-decalones 39 and 40 as probes, the importance of electrostatic effects



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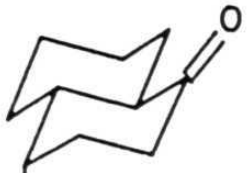

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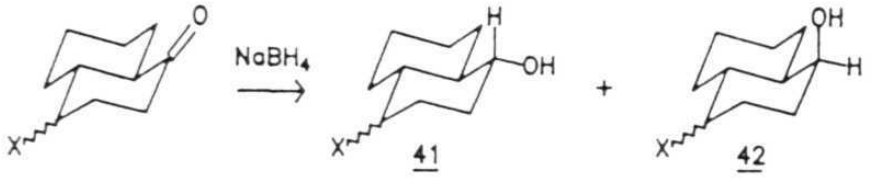
Table 3:[16]

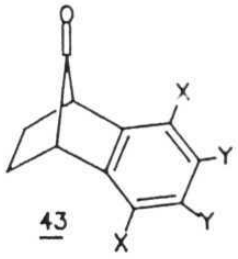


	X	% 41	% 42
1.	H	60	40
2.	eq OH	61	39
3.	eq OAc	71	29
4.	eq Br	66	34
5.	eq Cl	71	29
6.	ax OH	85	15
7.	ax OAc	83	17
8.	ax Cl	88	12
9.	ax F	87	13

was demonstrated. The results obtained reveal that the effects of various substituents on the stereoselectivity are strongly dependent upon the group orientation (axial *vs*

equatorial). The 4-axial substituents have a considerable larger effect than the 4-equatorial substituents (compare entries 2-5 vs 6-9 in the Table 3). This does not agree with the Cieplak model because the equatorial disposition of a substituent is well suited for participation in the Cieplak-type hyperconjugative interactions where as axial substituent is not. These results along with the other results reported earlier in the literature were rationalized by the author in terms of electrostatic effects in combination with torsional strain (Felkin-Anh model). The results were also supported by ab initio MO calculations.

Okada et.al considered a series of substituted 43[29] and 44[30] as probes to evaluate the origin of π-facial selection anticipating homoconjugation interactions to play a role in these systems. Reductions of 43 and 44 were carried out by employing various metal hydrides and the results obtained reveal that electron donating substituents on the benzene ring increases the proportion of anti attack (e.g. from 0 when X=Y=F to 55 when X=OMe, Y=H in 43 and from 57 when X=Y=F to 87 when X=OMe, Y=H in 44). The results agree with the transition state model proposed by Cieplak. Alternative explanation involves the contribution of the non-classical carbocation in the transition state as shown in 45 and 46.



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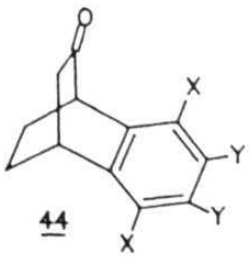

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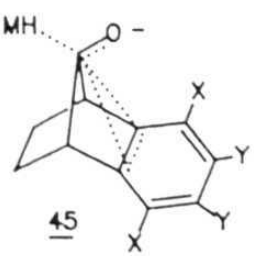
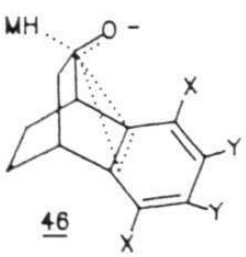


45



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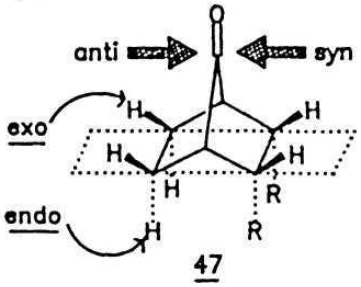
Present work: choice of the probe system:

The brief background described above indicates that the knowledge of the origin of face selectivity continue to be a subject of animated debate and discussions. Earlier work and some of the recent work involves cyclohexane based systems as probes despite the intrinsic flaw that the two π-faces of the trigonal center in these systems, e.g. cyclohexanone and methylenecyclohexane, are sterically non-equivalent (axial vs equatorial approach). Also, in most cases, same body of experimental data has been rationalized by various models having conceptual differences. Experimental data to directly test the validity of a model keeping all other effects (except those considered in that model) at minimum and to distinguish clearly between the predictions of one model from the other is a difficult task and such examples are scarcely available in the literature. This obviates the need for the design of new probes which can provide better insight into the problem of face selection. Our search for such systems led us to recognize 7-norbornyl and related systems as excellent substrates ideally suited for studying face selectivity. These systems offer sterically neutral environment around the reaction site with a provision of electronic tuning through endo-substituents. Some additional advantageous structural features of 7-norbornyl system are: (a) the C_7 sp^2 carbon in these systems is elevated above the $C_2C_3C_5C_6$ plane while the endo substituents lie below this plane, i.e. on the blind side of the

approach to the C_7 center (see 47), (b) the endo R group can be electronically fine tuned without perturbing the steric environment around C_7, and (c) the conformational rigidity



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and well documented reactivity pattern of 7-norbornyl systems.

In the Results and Discussion section that follows, we narrate our efforts directed towards evaluation and understanding of the origin of the π-facial diastereoselection in endo-substituted norbornyl and related systems. In this study, we have studied nucleophilic additions to endo-monosubstituted and endo, endo-disubstituted 7-norbornanones, 7-norbornenones and bicyclo[2.2.2]octan-2-ones. Few other related polycyclic systems containing norbornyl frameworks have also been studied. Electrophilic additions have been studied with various endo-substituted 7-methylene and 7-isopropylidene norbornanes. Thus, the research effort embodied in this thesis includes synthesis and characterization of the above described probe systems; nucleophilic (H^- or CH_3^-) and electrophilic [BH_3, per-acid, $Hg(OAc)_2$, IO_2, Br^+, etc.] additions to the appropriate derivatives; determination of the product distribution in each case employing a suitable technique and isolation and unambiguous stereochemical assignments to each of the diastereomeric

addition products. In addition, a critical evaluation of factors such as electrostatic effects, orbital interactions and ground state geometric distortions controlling the selectivities are also presented.

II. RESULTS AND DISCUSSION

The 'Results and Discussions' section has been further divided into two sub-sections A and B. The Section A, which deals with nucleophilic additions, is organized under six main headings. The main headings 1-5 deal with the nucleophilic additions to: i) 2,3-endo,endo-disubstituted-7-norbornanones, ii) polycyclic systems containing norbornyl framework, iii) 5,6-endo,endo-disubstituted-7-norbornenones, iv) 2-endo-mono-substituted-7-norbornanones and 5-endo-mono-substituted-7-norbornenones and v) 5,6-endo,endo-disubstituted and endo-mono-substituted bicyclo[2.2.2]octanones.

The results of one-carbon ring expansion of 7-norbornanones, which do not resonate with the title of Section A but are relevant to the discussion of π-facial selectivities, are included as 'Appendix' and constitute the last subheading of Section A.

The Section B, which deals with electrophilic additions, is organized under three main headings. The first incorporates the results of electrophilic additions [m-CPBA, BH_3, $Hg(OAc)_2$] to 2,3-endo,endo-disubstituted-7-methylenenorbornanes. The second heading describes the additions of Br^+, CCl_2, $^1O_2$ and m-CPBA to 2-endo-7-isopropylidenenorbornanes. The third main heading deals with additions of CCl_2, $^1O_2$ and m-CPBA to 5-endo-7-isopropylidenenorbornenes.

SECTION-A: NUCLEOPHILIC ADDITIONS TO NORBORNYL AND RELATED SYSTEMS

II.1 2,3-endo,endo-DISUBSTITUTED-7-NORBORNANONES:

Changes in electronic properties of a stereogenic center without accompanying changes in steric interactions at that site offer an important method to probe stereoelectronic effects. The endo-derivatives of 7-norbornanones appeared to us to be excellent substrates for this purpose. The symmetrically disposed endo-groups in 2,3-disubstituted 7-norbornanones provide a convenient means of electronic fine tuning through a variation in their electronic nature without concomitant change in the steric environment around the reaction center. The presence of only two intervening σ bonds between the substituent and the targeted site (C_7 carbonyl) in norbornyl derivatives is perhaps an example of remotest placement of the substituent with least separation one can conceive of any system! The simultaneous deployment of two electronically tunable groups on the blind side and at topographically equivalent positions from the reaction site is another distinctive feature which in our perception make norbornyl systems unique probes.

Although the basic norbornane skeleton may be assembled in one synthetic operation via the well known strategy of Diels-Alder reaction between an appropriate cyclopentadiene and a dienophile, not many endo-derivatives of 7-norbornanone are reported in the literature. Hence, we developed a

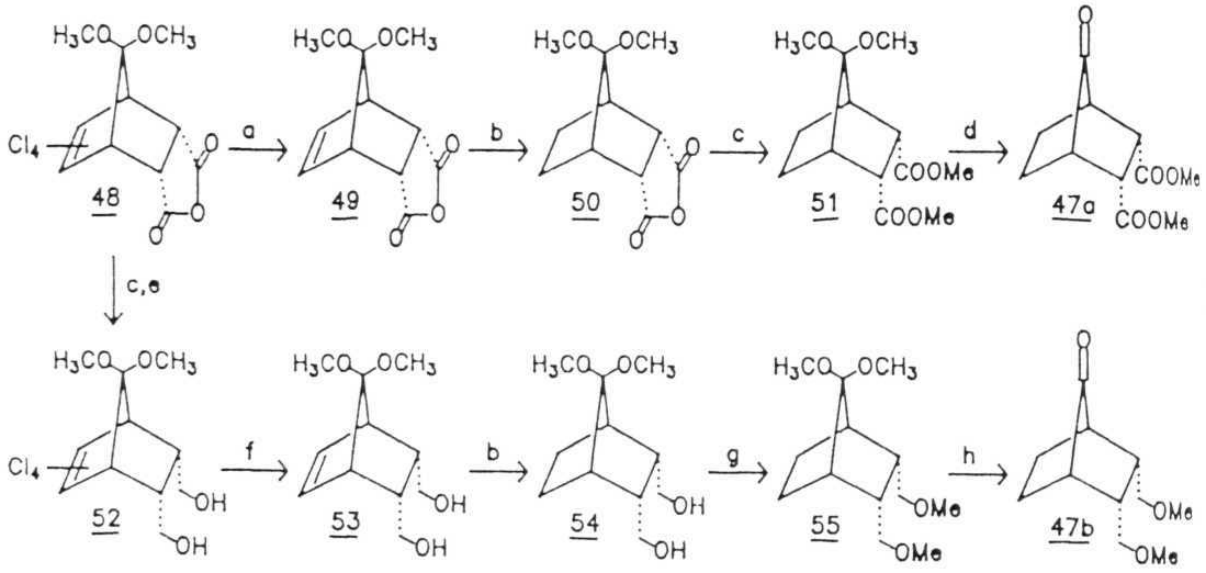
new procedure for the synthesis of several endo-substituted 7-norbornanone derivatives by executing simple functional group transformations on the known Diels-Alder adduct 48 between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and maleic anhydride.[31]

Synthesis of 2,3-endo, endo-disubstituted 7-norbornanones:

For the synthesis of endo, endo-disubstituted 7-norbornanones, Scheme 1, 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and maleic anhydride were identified as abundantly available starting materials. Diels-Alder reaction between them furnished a single endo-adduct 48.[31] A modified metal-NH_3 reduction procedure[32] was followed for reductive dehalogenation of the adduct 48 to furnish the unsaturated anhydride 49 upon direct crystallization in 30% yield. The presence of carbonyl absorptions due to an anhydride moiety at 1860 and 1780 cm^{-1} in the IR spectrum, appearance of signals corresponding to olefinic and bridgehead protons at δ 6.30, 3.64, respectively, in the ^1H NMR and a 7 line ^{13}C NMR spectrum indicated the structure 49. Catalytic hydrogenation of the endocyclic double bond of 49 furnished the anhydride 50 which on subsequent esterification led to diester ketal 51. Its ^1H NMR indicated the presence of a sharp singlet corresponding to two ester methyl groups and ^{13}C NMR showed an 8 line spectrum. Chemoselective hydrolysis of the ketal moiety in 51 gave diester ketone 47a in 72% yield as a low melting solid. Its IR spectrum showed carbonyl absorption at 1770 cm^{-1}, characteristic for 7-nor-

bornanones; ^1H NMR showed disappearance of -OMe signals of the ketal moiety and a 6 line ^{13}C NMR showed the carbonyl carbon resonance at δ 210.48. The diester ketone 47a exhibited great propensity to form a hydrate upon exposure to moisture as evidenced by its IR spectrum and variation in melting point on storage.

SCHEME 1



Reagents: a)Na-Liq.NH_3, THF, EtOH, NH_4Cl; (b) H_2, Pd-C, EtOAc, 20 psi; (c) MeOH/H^+, reflux, 5-6 h; (d) 5% aq.H_2SO_4, THF reflux, 1.5h; (e)$LiAlH_4$, ether, reflux, 10-12h; (f) Na-Liq.NH_3, THF, NH_4Cl; (g) NaH, MeI, THF, r.t.,45 min; (h) amberlyst-15, aq.acetone.

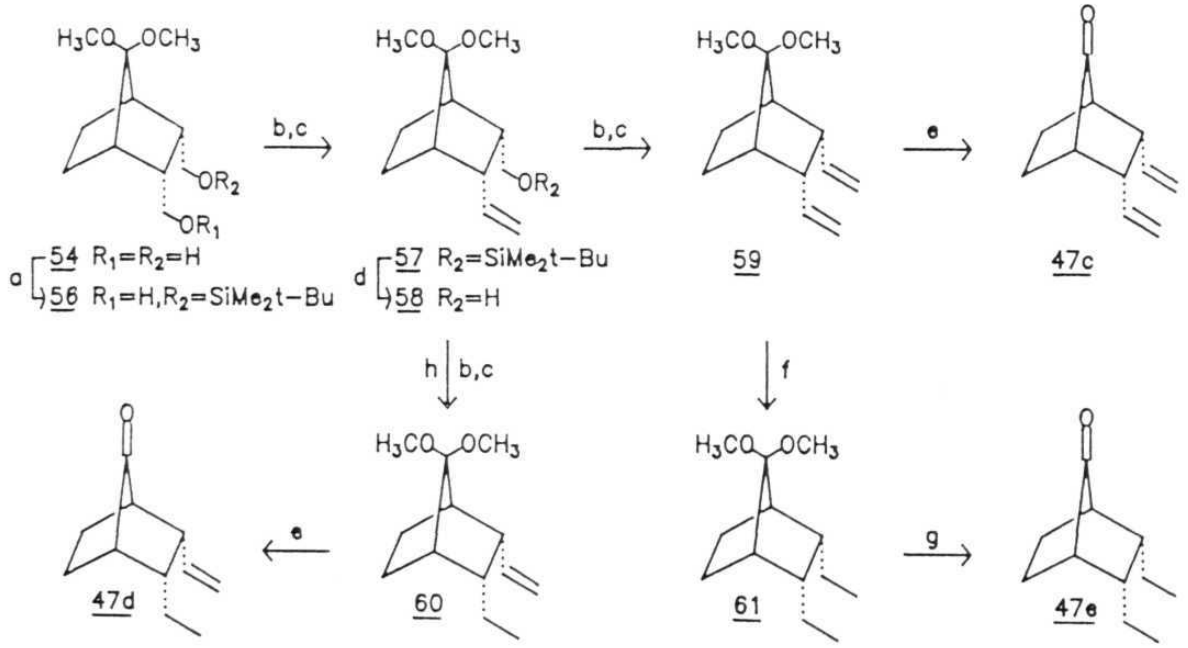
The dimethoxy derivative 47b was synthesized as shown in Scheme 1. Esterification of the adduct 48 and subsequent reduction of the diester[33] with lithium aluminium hydride furnished the diol 52[34] in 70% yield. Reductive dehalogenation of 52 using Jung's procedure,[35] furnished unsaturated

diol 53. Quantitative catalytic hydrogenation of endocyclic double bond in 53 followed by O-alkylation of the product 54 using NaH and MeI resulted in the formation of bis-methoxymethyl ketal 55. Careful hydrolysis of 55 with amberlyst-15 in refluxing acetone furnished the ketone 47b in 70% yield. The characteristic carbonyl absorption of 7-norbornanone at 1780 cm^{-1} in the IR spectrum, disappearance of -OMe signals of the ketal moiety in the ^1H NMR and a 6 line ^{13}C NMR spectrum with carbonyl carbon resonance at δ 215.13 secured structure 47b.

Synthesis of ketones 47c-e is delineated in Scheme 2. Sequential introduction of the vinyl groups on way to 47c necessitated the monoprotection of diol 54. This was accomplished by treatment of the diol 54 with an equivalent of NaH and subsequent quenching of the monosodium salt of 54 with TBDMSCl to yield monoprotected alcohol[36] 56 in 80% yield. Swern oxidation[37] of mono alcohol 56 followed by Wittig reaction gave olefin 57 in 60% yield. The ^1H NMR of 57 showed olefinic signals at δ 6.06-5.64 and 5.16-4.90 in a ratio of 1:2, characteristic of a vinyl group. Following deprotection, another round of Swern oxidation and olefination produced the desired divinyl ketal 59 in 51% yield as a mixture of endo, endo and exo, endo isomers (indicated by ^1H NMR of 59). In the transformation 54 ---> 59, some amount (ca.20-30%) of epimerization at C_2 or C_3 had occurred probably during the Wittig reaction. Fortunately, the two isomers could be resolved and were separated by column

chromatography using $AgNO_3$ impregnated silica gel. The stereochemistry of the required endo, endo-isomer 59 was secured through incisive analysis of its ^1H and ^{13}C NMR (8 lines) data which corresponded to a symmetrical structure. Further discussion on the assignment of endo-stereochemistry to substituents based on spectral evidence will follow under the next subheading. Deprotection of the ketal moiety in 59 was realized through amberlyst-15 in moist acetone to give ketone 47c in 60% yield. Diagnostic carbonyl absorption at

SCHEME 2



Reagents: (a) TBDMSCl, NaH, THF, r.t., 1.5h; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C, 30 min; (c) $Ph_3P^+CH_3Br^-$, t-$C_5H_{11}O^-Na^+$, C_6H_6, r.t., 30 min; (d) $(n\text{-}Bu)_4N^+F^-$, THF, r.t., 1h; (e) amberlyst-15, aq. acetone, reflux, 5-6h; (f) H_2, PtO_2, EtOAc, 40 psi, 20 min ; (g) amberlyst-15, aq. acetone, r.t., 12h; (h) H_2, Pd-C, EtOAc, 40 psi, 45 min.

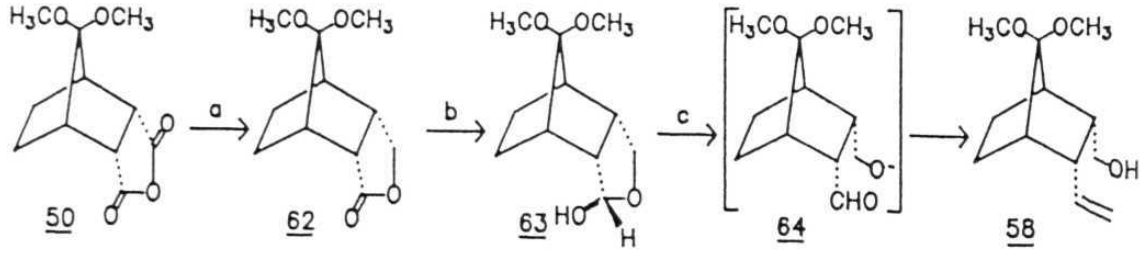
1770 cm^{-1} in the IR spectrum, two olefinic signals in a ratio of 1:2 in the ^1H NMR spectrum and a 6 line ^{13}C spectrum with carbonyl carbon resonance at δ 215.07 confirmed the structure 47c.

The endo,endo-2-ethenyl-3-ethyl derivative 60 was obtained by hydrogenating 58 followed by executing another round of oxidation and olefination sequence, Scheme 2. Amberlyst-15 catalyzed hydrolysis of the ketal moiety in 60 led to the ketone 47d in 60% yield, which was characterized by carbonyl absorption at 1760 cm^{-1} in the IR spectrum and satisfactory ^1H and ^{13}C spectral data.

The divinyl compound 59 on catalytic hydrogenation using PtO_2 as catalyst furnished the diethyl derivative 61 in quantitative yield. The ^1H NMR of 61 showed a triplet at δ 0.76 due to methyl resonance of $-CH_2\underline{Me}$ group. Deprotection of the ketal moiety with amberlyst-15 gave the ketone 47e in 80% yield, Scheme 2. Carbonyl absorption at 1770 cm^{-1} in the IR spectrum and a methyl triplet at δ 0.76 in the ^1H NMR and a 6 line ^{13}C NMR with carbonyl resonance at δ 217.24 fully supported the structure 47e.

To avoid the use of expensive TBDMSCl reagent as protecting group for alcohol (e.g., 54) and the circuitous route involved in the preparation of ketones 47c-e, an alternative sequence was sought. We considered and successfully executed a new route depicted in Scheme 3. The anhydride 50 obtained previously was smoothly converted into

SCHEME 3



Reagents: (a) $NaBH_4$, THF, 0-15°C, 45 min., (b)Dibal-H, CH_2Cl_2, -78°C, 15 min, (c) Ph_3PCH_3Br, Benzene, NaO^tAm, r.t., 30 min.

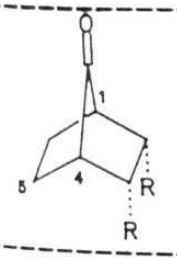
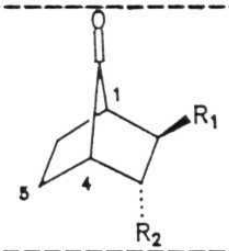
lactone 62 in 70% yield by selective reduction with $NaBH_4$. The crystalline lactone 62 showed strong lactone carbonyl absorption at 1780 cm^{-1} in the IR spectrum. The methylene protons in the lactone ring appeared at δ 4.44-4.16 in the ^1H NMR and lactone carbonyl resonance in the ^{13}C NMR was observed at δ 178.65. Dibal-H reduction of lactone[38] 62 at -78°C gave lactol 63 in 78% yield, which was used without purification in the next reaction. The lactol 63 is actually an internally protected hemiacetal of the aldehyde precursor for the synthesis of 58. Under the basic conditions of Wittig reaction, the hemiacetal 63 opens up[38] into the aldehyde intermediate 64 to furnish 58 in 71% yield, as shown in Scheme 3. The vinyl alcohol 58 is an advanced intermediate for the synthesis of all the three ketones 47c-e, see Scheme 2. This route (Scheme 3) efficiently utilizes an internal protection strategy to avoid the use of external protecting group and eliminates the repetition of oxidatio

step with the added advantage of handling solid intermediates. The observation that no epimerization at C_2 or C_3 center of 58 had occurred makes this route superior to the earlier one.

Stereochemistry of substituents in ketones 47a-e:

The stereochemical assignments to the key endo substituted ketones 47a-e follow from the unambiguous syntheses as well as ^{13}C NMR data.[39] The chemical shifts in ^{13}C NMR of norbornyl systems are sensitive to the orientation (exo vs endo) of the substituents,[39] a consequence of steric crowding and the effect is particularly more pronounced on a γ-carbon relative to the substituent. The C_2-endo substituent in these systems is known to shield the C_6(γ) carbon compared to unsubstituted parent compound due to γ-steric compression effect. Similarly, C_3-endo substituent would

Table 4. ^{13}C NMR resonances of $C_{5,6}$ in 7-norbornanones.

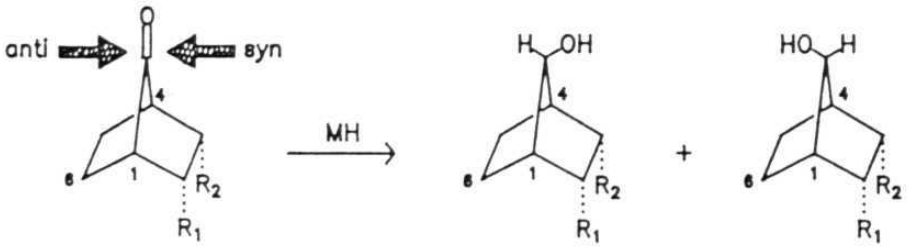
	$C_{5,6}$		C_5	C_6
1. R=H[40]	δ 24.12	6. R_1=Ethyl; R_2=H[40]	δ 23.34	23.34
2. R=COOMe	18.41	7. R_1=R_2=Vinyl[41]	16.58	23.82
3. R=CH_2OMe	16.76	8. R_1=Methyl; R_2=H[40]	23.38	23.38
4. R=Vinyl	17.41			
5. R=Ethyl	16.11			

shield C_5 resonance relative to the parent compound. When the C_2, C_3-substituents are exo-, C_5, C_6 carbon resonances are unaffected whereas C_7 carbon experience the shielding effect (γ-effect). Table 4 lists the ^{13}C chemical shifts of C_5, C_6 carbons of parent 7-norbornanone (entry 1) as well as ketones 47a-c,e (entries 2-5). The consistent shielding of C_5,C_6 resonances by about 6-8 ppm relative to parent compound confirms the endo disposition of the substituents.

Methyllithium additions and metal hydride reductions of the ketones 47a-e:

Reduction of 47a-e with $NaBH_4$, $LiAlH_4$ and the bulky $Li(Ot\text{-}Bu)_3AlH$ furnished a mixture of syn-65a-e and anti-66a-e alcohols in each case in nearly quantitative yield, Scheme 4.[42] Addition of methyllithim to 47a-c,e also furnished a mixture of syn-67a-c,e and anti-68a-c,e tertiary alcohols in high yield, Scheme 5.[42] The ratios of

Scheme 4



47a R_1=R_2=COOMe

47b R_1=R_2=CH_2OMe

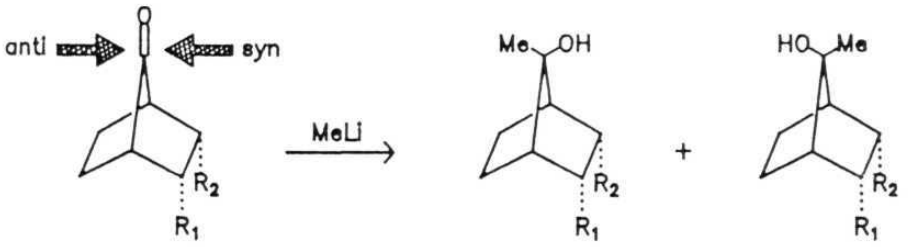
47c R_1=R_2=Vinyl

47d R_1=Vinyl,R_2=Ethyl

47e R_1=R_2=Ethyl

syn-65a-e anti-66a-e

Scheme 5



47a R_1=R_2=COOMe syn-67a-c,e anti-68a-c,e

47b R_1=R_2=CH_2OMe

47c R_1=R_2=Vinyl

47e R_1=R_2=Ethyl

syn : anti alcohols in each case were determined from the ^1H NMR integration of the crude mixture and the results are summarized in Table 5. All the diastereomeric pairs of alcohols were separated using silica gel column chromatography. Although some of the diastereomeric mixtures were poorly resolved on tlc plates, column chromatographic separation could be achieved by using long, narrow columns with large excess of substrate : silica gel ratio (ca. 1 : 200 to 400). Interestingly, syn-alcohols almost always eluted out first from the silica gel column (elution with appropriate ratio of ethyl acetate hexane solvent system) and this behaviour too can be of some diagnostic value in identifying the diastereomers.

Reduction of diester ketone 47a with $NaBH_4$ furnished a mixture of syn-65a and anti-66a with later being the major product (16 : 84). Lithium aluminium hydride also gave

similar result. In the case of lithium tri-tert-butoxyaluminium hydride a slight increase in the formation of syn-65a was observed but the major product still remained the same as in the case of other metal hydrides. Methyllithium addition to ketone 47a occurred almost exclusively from the

Table 5. Product ratios in the metal hydride reduction and methyllithium additions to 47a-e.

	syn : anti distribution[a]			
Substrate	$NaBH_4$[b,c]	$LiAlH_4$[b,c]	$(t\text{-}BuO)_3LiAlH$[b,c]	CH_3Li[d]
47a	16 : 84 (65a)(66a)	13 : 87 (65a)(66a)	23 : 77 (65a)(66a)	<10 : >90 (67a)(68a)
47b	60 : 40 (65b)(66b)			66 : 34 (67b)(68b)
47c	64 : 36 (65c)(66c)	65 : 35 (65c)(66c)	66 : 34 (65c)(66c)	73 : 27 (67c)(68c)
47d	75 : 25 (65d)(66d)			
47e	80 : 20 (65e)(66e)	79 : 21 (65e)(66e)	71 : 29 (65e)(66e)	83 : 17 (67e)(68e)

a Ratios based on ^1H NMR integration of the total mixture (+5%); b Reductions were carried out at ~0-10°C for 10 min-1h until the starting ketone was fully consumed. Reactions were continuously monitored by tlc; c In Methanol; d In dry diethyl ether.

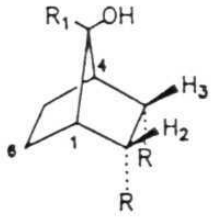
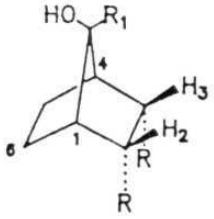
syn-face leading to anti-tertiary alcohol 68a. The ^1H NMR spectrum of the crude methyllithium addition product did not show peaks corresponding to syn-67a. The dimethoxy derivative 47b on $NaBH_4$ reduction produced a mixture of syn : anti alcohols in 60 : 40 ratio. The stereoselectivity found in this case, even though modest, is reverse of what is found in diester ketone 47a. The nucleophile approaches 47b preferentially from the anti-face and a marginal increment in this selectivity is observed during methyllithium addition. The divinyl substrate 47c shows same selectivity as 47b with further enhancement in the anti-face attack with all the metal hydrides studied. Methyllithium addition to 47c takes place with relatively greater preference for anti-attack as compared to hydride reduction. Ethyl vinyl derivative 47d shows intermediate selectivity between divinyl 47c and diethyl 47e. The highest anti preference in the series 47a-e during metal hydride reduction and methyllithium addition was observed for the diethyl derivative 47e.

Stereochemistry of syn-65a-e, 67a-c,e and anti-66a-e, 68a-c,e alcohols:

The diastereomeric mixture of syn- and anti-alcohols in each case was separated and fully characterized. The stereochemistry of alcohols produced during the metal hydride reduction and methyllithium addition was unambiguously assigned on the basis of incisive analysis of ^1H NMR data. The well known deshielding effect of C_7 hydroxyl group on the exo-protons beneath it, in the norbornyl and related

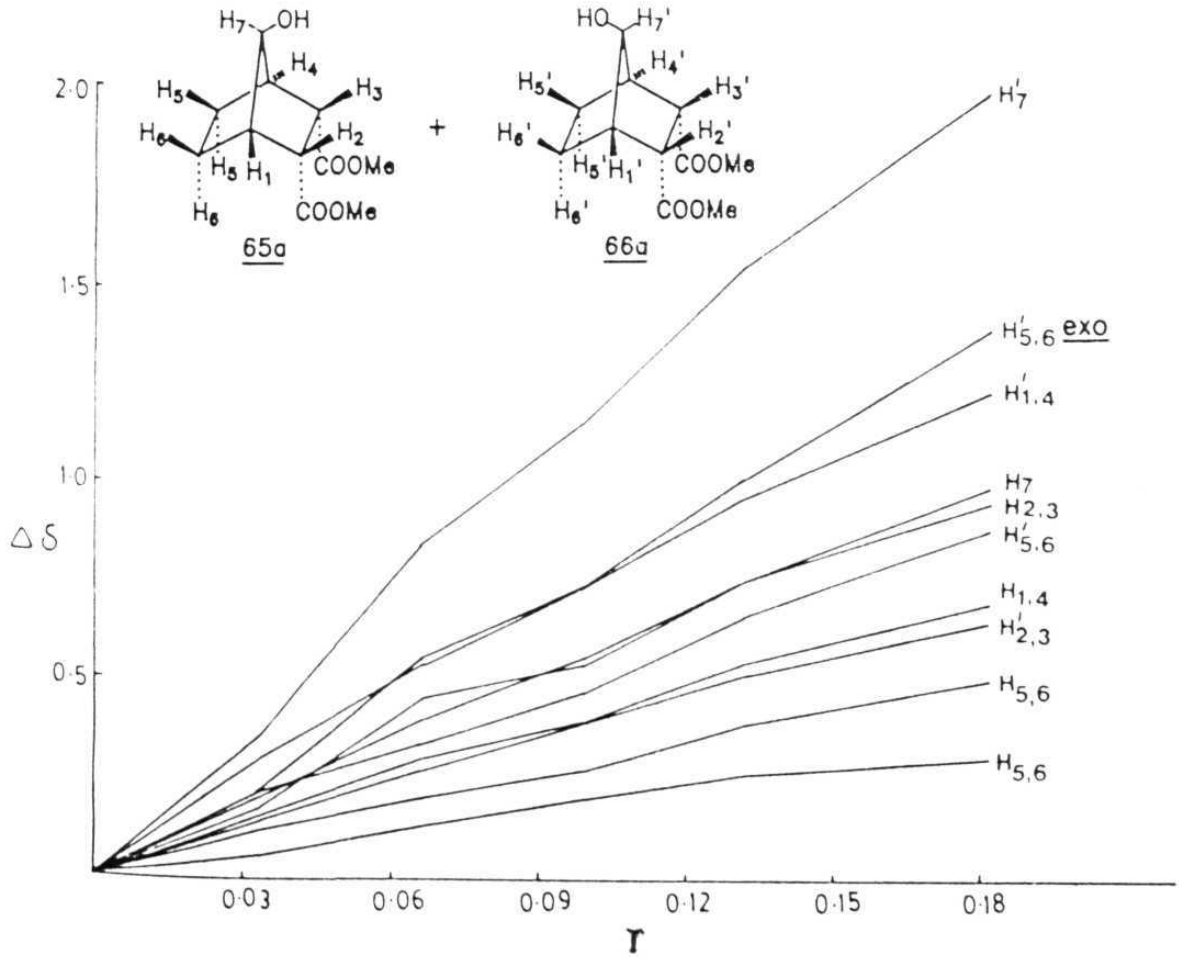
systems was used to differentiate syn-and anti-isomers. Hydroxyl group at C_7 in syn-alcohols deshields the C_2, C_3 exo-protons by about 0.3-0.4 ppm compared to the chemical shift of the same protons in the anti-series of alcohols. Similarly, C_5, C_6 exo-protons were relatively deshielded by the same magnitude in anti-alcohols. Table 6 lists the chemical shifts of exo-H_2,H_3 protons of both syn- and anti series of alcohols. The spectra of some of the key compounds as well as of diastereomeric mixture are shown in Section V (Figs.1-15) of this thesis.

Table 6. ^1H NMR resonances of $H_{2,3}$ in syn- and anti-7-norbornanols.

		exo-$H_{2,3}$		exo-$H_{2,3}$
1. R=COOMe	R_1=H	δ 3.46	R=COOMe	R_1=H δ 2.98
	R_1=Me	3.57		R_1=Me 3.10
2. R=CH_2OMe	R_1=H	2.66	R=CH_2OMe	R_1=H 2.25
	R_1=Me	2.76		R_1=Me 2.35
3. R=Vinyl	R_1=H	3.08	R=Vinyl	R_1=H 2.68
	R_1=Me	3.22		R_1=Me 2.82
4. R=Ethyl	R_1=H	2.12	R=Ethyl	R_1=H 1.80
	R_1=Me	2.28		R_1=Me 1.92

In order to further confirm the configuration of alcohols, lanthanide shift reagent (LSR) studies[43] using $Eu(fod)_3$ were carried out. It is well known that the magnitude of shifts produced by added LSR depends on geometric factors. Hence, analysis of the lanthanide induced shifts thereby produced provides valuable information concerning the stereochemistry of the molecules, particularly in rigid bicyclic systems. Inspection of structures of <u>syn</u>-<u>65a-e</u>,

Fig.VII. The effect of the concentration ratio r [where r =(LSR)/(<u>syn</u>+<u>anti</u> alcohol)] on the magnitudes of the individual proton shifts ($\Delta\delta$ for H_1-H_7 and H_1'-H_7') of mixture of alcohols derived from the reduction of ketone <u>47a</u>



67a-c,e and anti-66a-e, 68a-c,e alcohols suggest that H_2, H_3 exo-protons in syn-alcohol should feel maximum deshielding effect compared to any other proton. In a complementary sense, relatively larger shift changes should be expected for H_5, H_6 exo-protons in anti-alcohols. Further, H_7 proton in both the series is expected to show larger shifts because of its geminal relationship to alcohol functionality. Increasing amounts of $Eu(fod)_3$ were added to a mixture of syn-65a and anti-66a alcohols and the effects of each addition on the chemical shifts were measured and the results are depicted in Fig.VII. It shows that H_7 of both syn-65a anti-66a alcohols (H_7 & H_7') has undergone largest $Eu(fod)_3$ induced shift. Among the remaining protons of each isomer, $H_{2,3}$ exo-protons of syn-65a and $H'_{5,6}$ exo-protons of anti-66a showed greater shifts. Further exo-$H'_{2,3}$ and exo-$H_{5,6}$ in the epimer in which these hydrogens are anti to the hydroxyl group, only marginal shift is observed (Fig.VII). Similar LIS studies were carried out for other epimeric pairs of alcohols to fully secure the stereochemical assignments.

Interpretation of results:

The results summarized in Table 5 demonstrate a very significant variation in face selectivity as a function of 2,3-endo,endo-substitution, the most dramatic being the reversal in syn : anti ratio in going from 47a (16 : 84) to 47e (80 : 20). Electron withdrawing groups such as -COOMe in 47a are directing the nucleophile from the syn-face

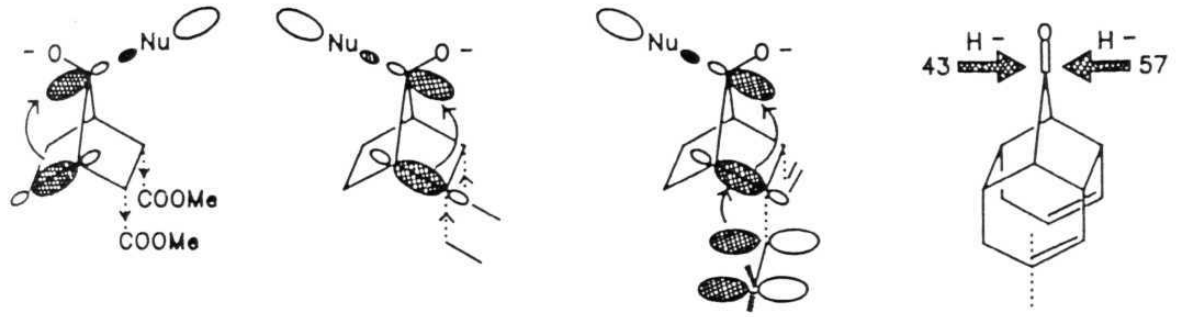
producing anti-alcohol 66a as the major product. On the other hand, electron donating alkyl substituents as in 47e are causing a complete cross-over in the selectivity by facilitating a predominant approach of the reagents from the anti-face resulting in the formation of syn-alcohol 65e in large excess.

The remote endo-substituents, being present on the 'blind side' of the reagent approach to the reaction center at C_7, seem to exercise control over the 'reagent traffic' at C_7 only through electronic influence since steric considerations can be ruled out in these rigid bicyclic systems 47a-e. Indeed, product ratios obtained in the addition reactions are insensitive to the steric bulk of the reagent. Several electronic factors have been previously reported to account for the selectivity during nucleophilic additions to cyclic ketones, particularly cyclohexanones (vide supra). Among the factors considered important and responsible for the selectivity in cyclohexane-based systems, few factors such as product development control, torsional strain, anti-periplanar interaction with axial hydrogen, steric effect of axial hydrogen at C_4, etc. do not exist for norbornanones 47a-e and may be ruled out at the outset. Hence, it is reasonable to speculate that orbital interactions or electrostatic influences may be the prime factors responsible for the observed selectivity in these systems.

The transition state model proposed recently by Cieplak[13] effectively incorporates orbital interactions and

can satisfactorily explain the results summarized in Table 5. According to this model, the delocalization of σ electrons in the electron rich anti-periplanar bonds into σ* orbital of the incipient C-Nu bond lowers the transition state energy. Hence, the transition state in which the nucleophile approaches from the side opposite to the most electron rich σ bonds is preferred over the other alternative transition state. The electron withdrawing groups in 47a render C_1-C_2 and C_3-C_4 σ bonds electron deficient relative to C_1-C_6 and C_4-C_5 bonds and the transition state of the syn-approach is stabilized by the electron delocalization from the electron rich anti- periplanar σ bonds in σ* orbital, as shown in 69. The electron donating substituents make C_1-C_2 and C_3-C_4 pair of σ bonds relatively electron rich favoring the transition state for the anti-approach as shown in 70. This explains the observed reversal in face selectivity when the substituents are changed from ester group to ethyl group.

The anti preference in the case of 47b and 47c, having groups traditionally considered as electron withdrawing (-I) is somewhat unexpected at first sight but may be attributed to through-space donation in a perpendicular conformation as shown in 71 for 47c. This view is confirmed by a recent report[44] from our laboratory on the $NaBH_4$ reduction of tetracyclic ketone 72 in which the two vinyl groups are locked and through-space donation in a perpendicular conformation is not possible. The observed selectivity in the

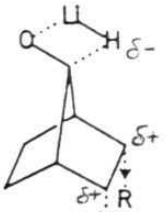


69 70 71 72

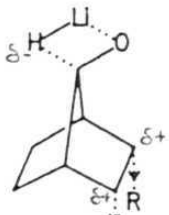
reduction of 72 is indicated on the structure. The mild electron withdrawing nature of vinyl substituent in 72 is reflected in the preferential approach of the hydride ion from the side bearing vinyl substituents. These results indicate that a free rotating vinyl substituent in norbornyl systems behaves like an electron donor group (perhaps by a through-space mechanism) and directs the preferential approach of the nucleophile from the anti-face. If the free rotation of the vinyl group is blocked (as in 72), it is restored back to its normal -I effect. When one substituent is vinyl and the other is ethyl as in ketone 47d, the observed selectivity is the average of what is observed for divinyl and diethyl derivatives 47c and 47e. The enhanced selectivity of methyllithium additions in all the cases is attributed to its greater nucleophilicity compared to hydride ion.

After the publication of our preliminary results, Houk and coworkers[16,45] have attempted to interpret our results on the 7-norbornanones 47a-e in terms of electrostatic interactions. The transition structures for a series of

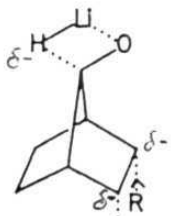
substituted-7-norbornanones were located using 3-21G basis set and were reoptimized by 6-31G* basis set. The calculations performed indicate that the relative stabilities of the transition states for syn and anti additions of LiH are largely determined by electrostatic interactions. Electron withdrawing substituents induce positive charge at C_2, C_3 and syn addition (73) is preferred due to favorable electrostatic interactions of the positive charge with the incoming negatively charged nucleophile (see 73 and 74). On the other hand, electron-donating substituents induce negative charge at C_2, C_3 and anti addition (75) becomes favorable (see 75 and 76). Further, it was argued that the anti-preference induced by the weakly electron withdrawing substituents such as hydroxy methyl (R=-CH_2OH) and vinyl is caused by electrostatic repulsions in the syn transition structure between the hydride and the electronegative OH or vinyl group. The argument for hydroxymethyl may be extrapolated to methoxy methyl (R = CH_2OMe) substrate 47b.



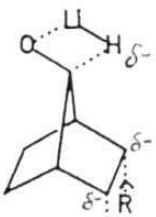
73 R



74 R



75 R

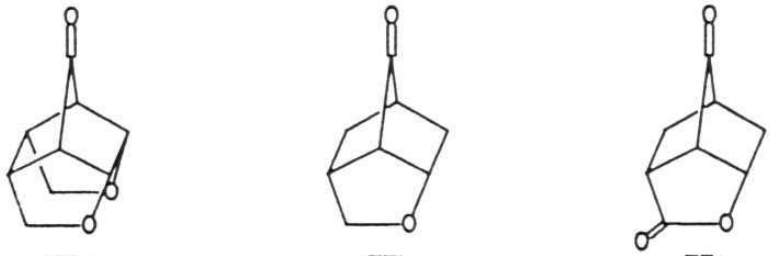


76 R

However, our additional experimental results as well as calculations and those of others[25a] do not fully accord with the interpretation (vide infra) based on the primacy of electrostatic effects.

II.2 POLYCYCLIC KETONES CONTAINING NORBORNYL FRAMEWORK:

The polycyclic ketones 77a-c attracted our attention because of the valuable insights that could be obtained from these systems on the selectivity induced by substituents which lock-in the $C_{2,6}$ and $C_{3,5}$ endo positions, thus removing any kind of steric interaction between the C_2, C_3 endo-substituents and the C_5, C_6 endo-hydrogens. Remote, facial discrimination can be achieved through the substituents on the endo bridges.



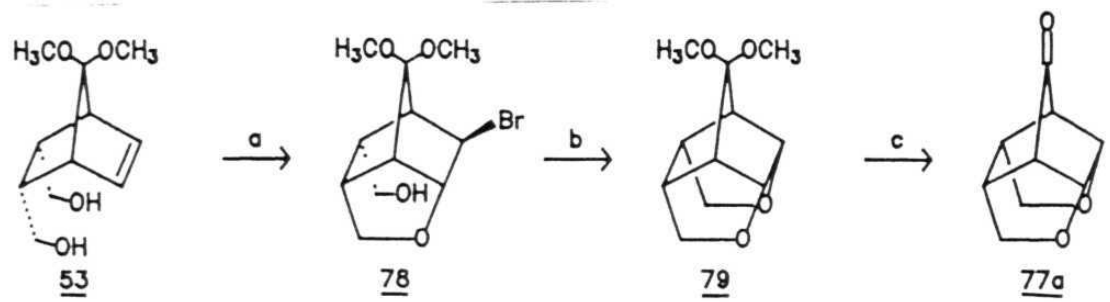
77a 77b 77c

Synthesis of ketones 77a-c:

Synthesis of 77a is depicted in Scheme 6. The unsaturated diol 53 on treatment with NBS in aqueous acetone produces bromo ether 78 in 92% yield through the intermediacy of bromonium ion and subsequent intramolecular nucleophilic opening by the primary alcohol group. The doublet at δ 4.62 of the exo-methine proton attached to ether oxygen in ^1H NMR and 11 signals in ^{13}C NMR supported the structure 78. The second cyclization via intramolecular nucleophilic displacement of bromine by alkoxide is effected in 66% yield by refluxing 78 with NaH in THF. The symmetric ketal 79 showed absorption at 1070 and 1050 cm^{-1} in the IR spectrum and a signal due to methine protons attached to ether oxygen at

δ 4.16 in the ^1H NMR spectrum. The two fold symmetry of 79 is further confirmed by 7 line ^{13}C spectrum. Hydrolysis of the ketal with amberlyst furnished ketone 77a in 81% yield. The characteristic carbonyl absorption at 1770 cm^{-1} in the IR spectrum and carbonyl carbon resonance at δ 208.2 in a 5 line ^{13}C confirmed the structure.

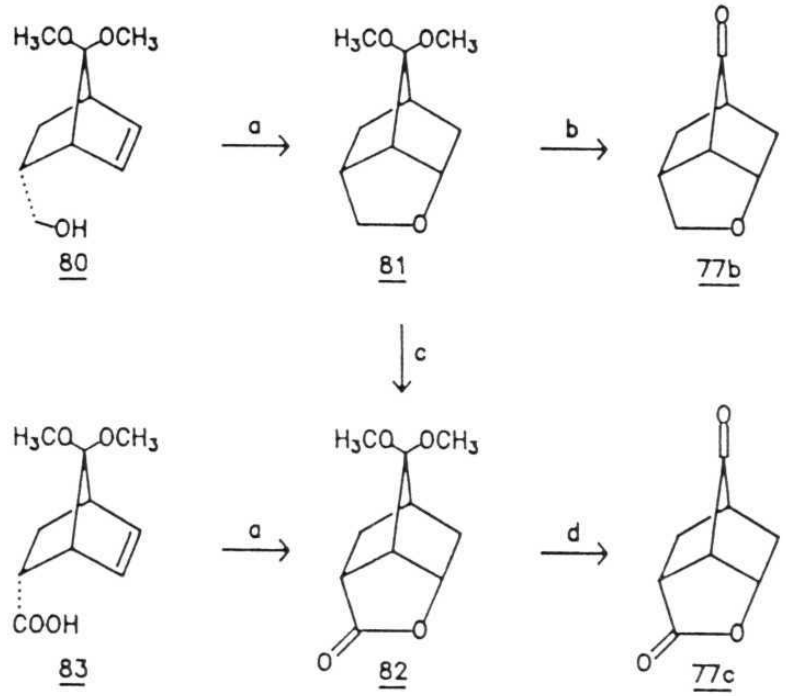
SCHEME 6



Reagents: a) NBS, aq.acetone, r.t., 12h; b) NaH, THF, reflux, 2h; c) Amberlyst-15, aq.acetone, reflux, 30 min.

Scheme 7 describes the synthesis of ketones 77b,c. Intramolecular nucleophilic opening of the mercurinium ion intermediate initially formed by treatment of 80[46] with $Hg(OAc)_2$ followed by demercuration with alkaline $NaBH_4$ furnished ketal ether 81 in 73% yield. The disappearance of olefinic signals and the presence of methine proton signal linked to ether oxygen at δ 4.42 in ^1H NMR is in agreement with the structural formulation 81. The ketal 81 upon hydrolysis using amberlyst afforded ketone 77b in 56% yield. The IR spectrum showed the carbonyl absorption at 1760cm^{-1} and the corresponding signal in ^{13}C spectrum appeared at δ 213.07. The lactone derivative 82 may be prepared either by oxymercuration-demercuration of acid 83[46] or by ruthenium

SCHEME 7



Reagents: a) $Hg(OAc)_2$, NaOH, $NaBH_4$, r.t., 40 min.; b) Amberlyst-15, aq.acetone, r.t., 6h; c) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O; d) H_2SO_4, CH_2Cl_2, r.t., 4h.

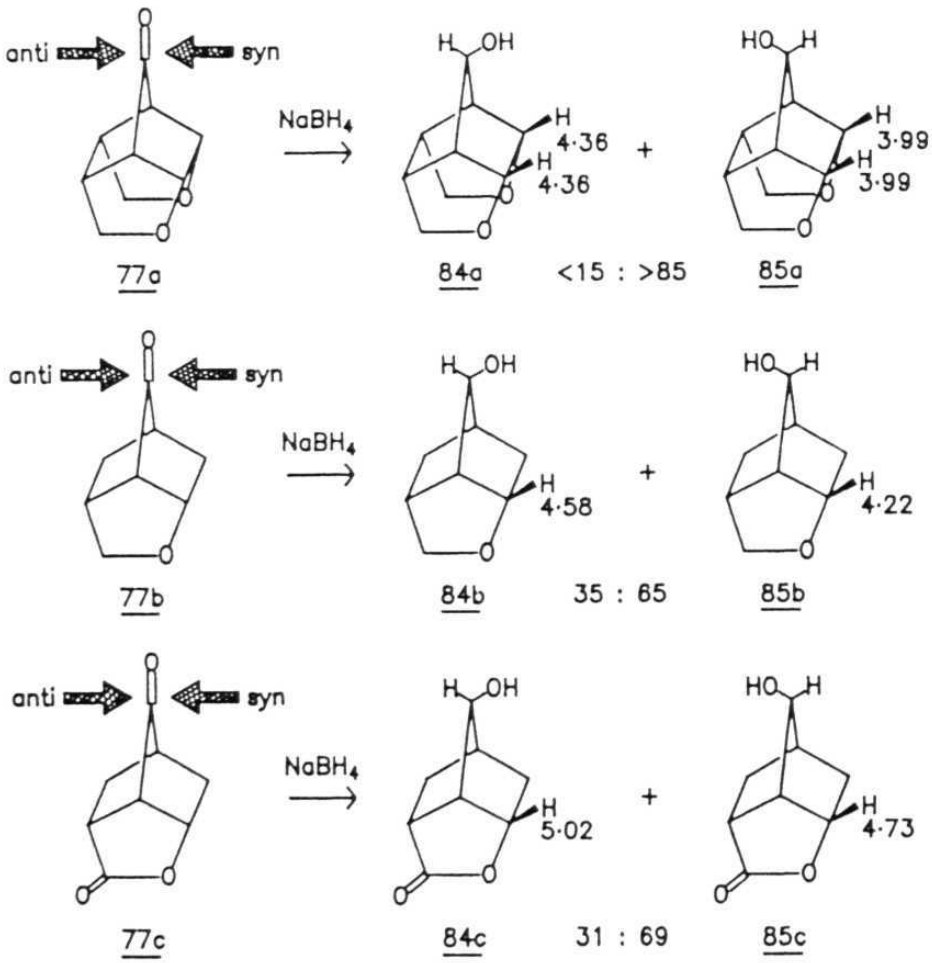
tetroxide oxidation[47] of 81 as shown in Scheme 7. The lactone carbonyl of 82 appeared at 1770 cm^{-1} in the IR spectrum. The ^1H NMR spectrum showed a signal at δ 4.83 corresponding to oxygen attached methine proton. The hydrolysis of ketal 82 could not be achieved under mild conditions. After several trials, catalytic amount of conc.H_2SO_4 in CH_2Cl_2 was found to give satisfactory yield (40%) of ketone 77c. The ketone 77c showed high propensity to form hydrate upon exposure to moisture. The IR spectrum showed strong absorption at 1760 cm^{-1}. The ^1H NMR spectrum indicated the presence of oxygen attached methine proton at

δ 5.02. The ketone and lactone carbonyl resonances appeared at δ 208.83 and 178.77, respectively, in the ^{13}C NMR spectrum.

$NaBH_4$ reduction of ketones 77a-c:

Reduction of ketones 77a-c with $NaBH_4$ furnished a mixture of diastereomeric syn-84a-c and anti-85a-c alcohols[#] in high yield, Scheme 8. The ratios of the products were

SCHEME 8



[#] For the sake of convenience, syn and anti terminology is used with reference to C-O bond as indicated in Scheme 8.

determined from the ^1H NMR integration of the crude reaction mixture and are shown in Scheme 8. The diastereomeric pair of alcohols in each case were separated by means of column chromatography and fully characterized.

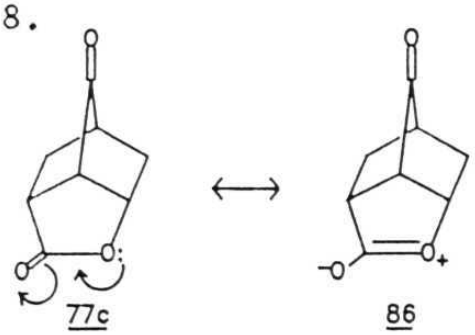
Stereochemistry of syn-84a-c and anti-85a-c alcohols:

The stereochemistry of the products in all the cases was determined unambiguously from the ^1H NMR spectra on the basis of greater deshielding of exo-methine protons attached to oxygen atom in syn-84a-c alcohols compared to the corresponding anti-85a-c alcohols (see, Figs.16-19 in Section V). The chemical shift values of these protons (in ppm) are indicated on the structures in Scheme 8.

Interpretation of results:

These results can also be readily reconciled in terms of the Cieplak's hyperconjugative model.[13] The endo C-O bonds in 77a act as electron withdrawing groups and the nucleophile approaches predominantly from the syn-face leading to anti-alcohol 85a (>85%). The ketone 77b with only one ether linkage at C_2 also shows syn-preference with a reduced selectivity as compared to 77a. The lactone carbonyl in 77c can act in two ways: (i) since it is attached to C_6, the C_1-C_6 bond may become relatively electron poor and the anti approach would be preferred, (ii) the carbonyl group can make the C-O bond attached to C_2 more powerful electron withdrawing group by contributing the resonance structure shown in 86. This should increase the

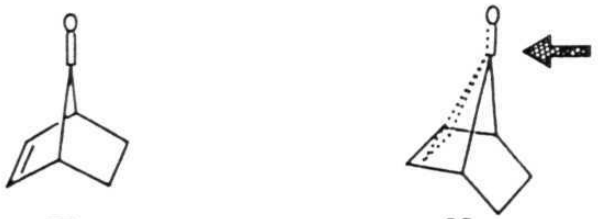
syn-preference. Thus, the two effects (i) and (ii) oppose each other and the net selectivity in 77c is similar to that of ether 77b, Scheme 8.



77c 86

II.3 5,6-endo,endo-DISUBSTITUTED-7-NORBORNENONES:

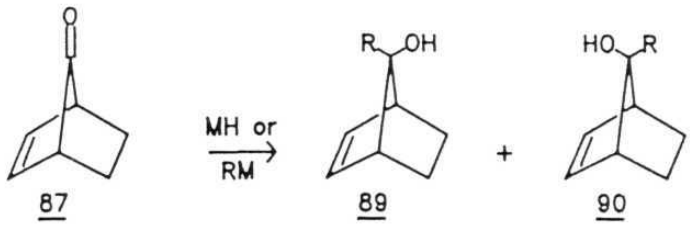
7-Norbornenone 87 is an intrinsically interesting substrate that has served as an important stereoelectronic probe in diverse organic reactions. Extensive studies by means of ^{13}C NMR,[48] PES[49] and CD[50] spectra have shown homoconjugative interaction between the endocyclic double bond and the carbonyl group of 87. The face selectivity during nucleophilic additions to these systems is expected to reflect the



87 88

homoconjugative interaction. Such interactions of the 7-keto group with the π electrons of the double bond would be expected to result in a preferred approach of the reagent from the anti direction (with respect to double bond) to give the syn-alcohol as shown in 88. Nucleophilic additions to 7-norbornenone with a variety of reagents have been reported in the literature and some of them are summarized in Scheme 9.

SCHEME 9



87 89 90

Reagent	Ratio		Ref.
$NaBH_4$	85	15	51
CH_3Li	74	26	52,53b
CH_3MgBr	96	4	53a
CH_2=CH Li	29	71	53b
C_6H_5Li	28	72	53b
C_6H_5MgBr	74	26	53b
CH_2=$CHMgBr$	80	20	54
C_2F_5Li	0	100	55
C_2F_5MgBr	4	96	55

Brown and Muzzio[51] made the observation that $NaBH_4$ reduction of 87 proceeds predominantly from the double bond side to furnish 85 : 15 mixture of anti-89 (R=H, Scheme 9) and syn-90 alcohols, respectively. Subsequently, Erman[52] as well as Warkentin[53] reported that CH_3Li and CH_3MgBr also exhibit marked preference for the syn face addition to furnish 89 ($R=CH_3$) as the major product. However, Warkentin noted[53b] that in the case of vinyl lithium and phenyl lithium addition to 87, there was reversal in face selectivity and syn-90 (R = vinyl or phenyl) was the major product. More recently, Gassman and O'Reilly[55] observed that C_2F_5Li

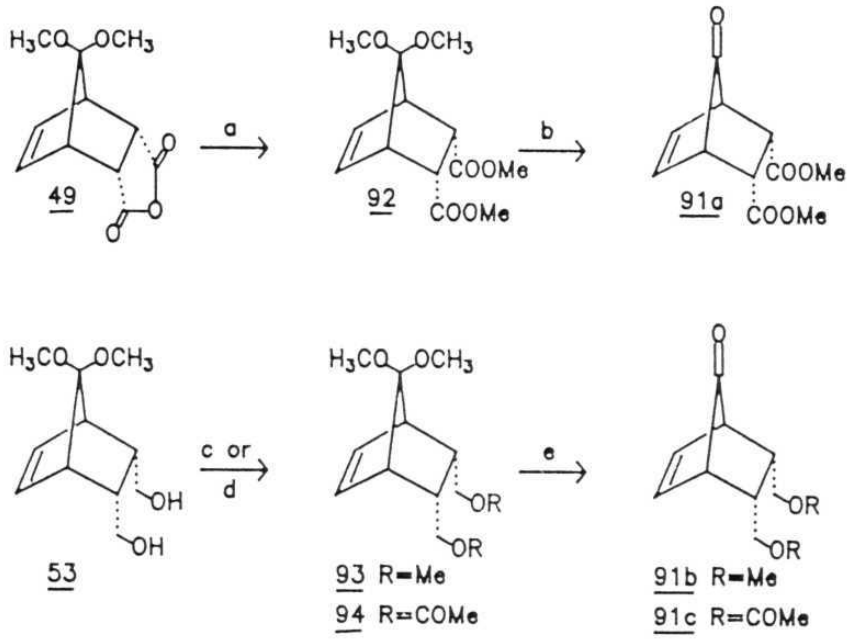
and C_2F_5MgBr added to 87 almost exclusively from the anti-face to furnish syn-90 ($R=C_2F_5$). These results on the face selectivity in nucleophilic additions to 87 demonstrate that the homoconjugative interaction of the type shown in 88 is not playing a decisive role in controlling the 'reagent traffic' at C_7. These results have been interpreted in terms of one or more of the following factors: (i) preference for the approach from the sterically more accessible syn-face,[51,53] (ii) steric bulk of the reagent; (iii) polar factors e.g. ion-pair formation through double bond participation at the C_7-electrophilic center;[52,53,24c] and (iv) nucleophilicity of the attacking reagent.[55]

The intriguing results discussed above promoted us to play the 'endo-substituent trick' on 7-norbornenone and to see whether the selectivity is altered or reversed by the remote substituents.[56]

Synthesis of endo,endo-disubstituted-7-norbornenones:

The ketones 91a-c were synthesized from the readily and easily available starting materials as shown in Scheme 10. Acid catalyzed esterification of anhydride 49 using dry MeOH furnished diester 92 in 86% yield. The ^1H NMR spectrum showed a sharp singlet at δ 3.54 due to ester methyl groups. Careful ketal hydrolysis of 92 afforded the highly crystalline ketone 91a in 75% yield. Two carbonyl absorption peaks at 1790 and 1735 cm^{-1} in the IR spectrum, disappearance of ketal proton signals in the ^1H NMR spectrum and a δ

SCHEME 10



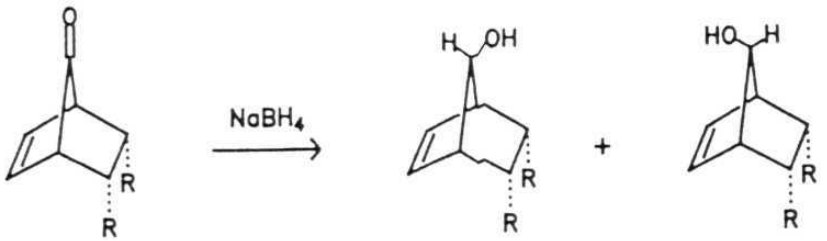
Reagents: a) MeOH, H^+, reflux. 5h; b) 5% aq.H_2SO_4, THF, reflux, 30 min; c) NaH, THF, MeI, r.t., 45 min; d) Ac_2O, DMAP, CH_2Cl_2, r.t., 30 min.; e) Amberlyst-15, moist acetone, reflux.

line ^{13}C NMR spectrum with carbonyl resonance signal at δ 198.30 confirmed the structure 91a. The dimethoxy derivative 93 was obtained by MeI alkylation of sodium salt of the diol 53 formed on its treatment with NaH. Acid catalyzed hydrolysis of 93 furnished the desired ketone 91b in 93% yield. Acetylation of the diol 53 using Ac_2O and DMAP followed by ketal hydrolysis furnished diacetate ketone 91c as a crystalline solid. The ^1H NMR spectrum of 91c indicated the presence of a sharp singlet of acetate methyl groups at δ 2.06 and the ^{13}C spectrum showed a 7 line spectrum with carbonyl resonances at δ 202.06 and 170.77.

$NaBH_4$ reduction and methyllithim addition to 91a-c:

The $NaBH_4$ reduction of 91a-c[56] furnished a mixture of syn-95a-c and anti-96a-c alcohols# whose ratios were determined from ^1H NMR integration of crude mixture and glc analysis (Scheme 11). The diastereomers in each case were separated by silica gel column chromatography and fully characterized.

SCHEME 11

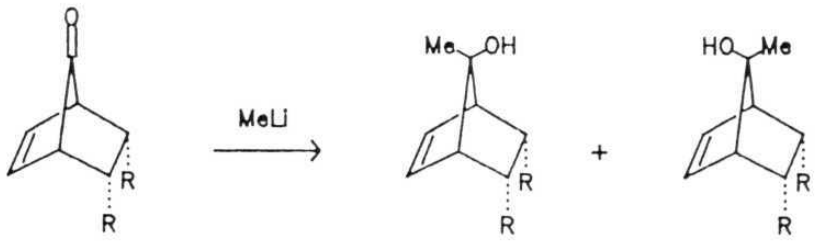


87	R=H	89	85 : 15	90
91a	R=COOMe	95a	45 : 55	96a
91b	R=CH_2OMe	95b	88 : 12	96b
91c	R=CH_2OAc	95c	87 : 13	96c

Methyllithium addition[56] to 91a and 91b also furnished a mixture of syn-97a,b and anti-98a,b tertiary alcohols in high yield, Scheme 12. The diastereomers in each case were once again separated by means of column chromatography and fully characterized.

For the sake of uniformity with earlier results on 7-norbornanones, syn and anti prefixes are used with reference to substituents.

SCHEME 12



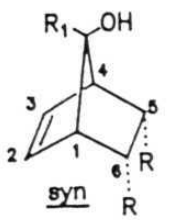
87	R=H	89	74 : 26	90
91a	R=COOMe	97a	10 : 90	98a
91b	R=CH_2OMe	97b	74 : 26	98b

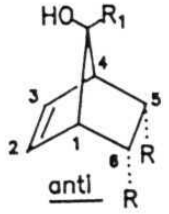
The results shown in Scheme 11 and 12 demonstrate significant variation (reversal) in the face selectivity when the substituents are -COOMe groups. This selectivity is much more pronounced in the case of CH_3Li addition. Methoxy methyl and acetoxymethyl substituents show very little change in the selectivity relative to the parent 87.

Stereochemistry of syn- and anti-alcohols:

The stereochemistry of the products in all the cases was determined unambiguously by the diagnostic deshielding effect of hydroxyl group on the protons beneath it (see, Figs.20-24 in Section V). The chemical shift values for three sets of protons for the products derived from $NaBH_4$ reduction and MeLi addition to 91a and 91b are given in Table 7. The trends of these shifts are similar to those reported for 7-norbornenols. Further evidence for the stereochemistry was obtained by hydrogenating all the unsaturated alcohols individually and comparing them with the alcohols obtained in the 7-norbornanone series, see Schemes 4 & 5 as well as Table 5.

Table 7. ^1H NMR resonances of $H_{2,3}$, $H_{1,4}$ and $H_{5,6}$ in syn- and anti-7-norbornenols.





		syn $H_{2,3}$	anti $H_{2,3}$	syn $H_{1,4}$	anti $H_{1,4}$	syn $H_{5,6}$	anti $H_{5,6}$
R=COOMe	R_1=H	6.14	6.28	2.92	3.16	3.56	3.28
	R_1=CH_3	6.18	6.34	2.72	2.90	3.74	3.42
R=CH_2OMe	R_1=H	6.03	6.16	2.72	2.95	2.72	2.51
	R_1=CH_3	6.04	6.22	2.52	(2.80-2.48)	(3.28-2.80)	(2.80-2.48)

Interpretation of results:

Incorporation of the endo-substituents in 7-norbornenone skeleton, in principle, should not alter the already existing steric bias in the system. The magnitude of alteration in the selectivity due to this intrinsic bias, among other factors, is reflected in the reactions of the parent ketone 87 (see Scheme 9). Any change in the selectivity by the introduction of endo-substituents can therefore be attributed to the electronic effects of the remote substituents. But, if the incorporation of the endo-substituents introduces distortions in the ground state geometry of the ketone, then factors such as unsymmetrical pyramidalization

of the carbonyl unit and torsional strain as suggested by Felkin-Anh model[9,10] may become the dominant factors controlling the face-selectivity. There are literature precedences[57] in other systems where ground state distortions have been invoked to account for the observed selectivities.

To solve this problem and to understand the origin of selectivity (geometric distortions vs electronic effects) in these systems, single crystal X-ray analysis[58] of 91a was carried out.# The molecular structure of 91a is shown in Fig.VIII. The important features of the structure relevant to the discussion of the observed π-facial selectivity are: (i) 7-keto unit is essentially planar (Σangles=360°). Therefore, pyramidal distortions do not determine the preferred approach of the nucleophile. (ii) the bridge hydrogens are eclipsed to the carbonyl (C=O) bond, hence, the Felkin-Anh torsional model also does not apply to the facial selectivity in the present system. (iii) The most substantial geometric distortion in 91a is the tilt of the 7-keto bridge away from the C=C bond by 6.2(1)° as shown in 99. This tilt makes the double bond side face of the carbonyl more accessible to the approaching nucleophile on steric grounds. However, the experimentally observed major product

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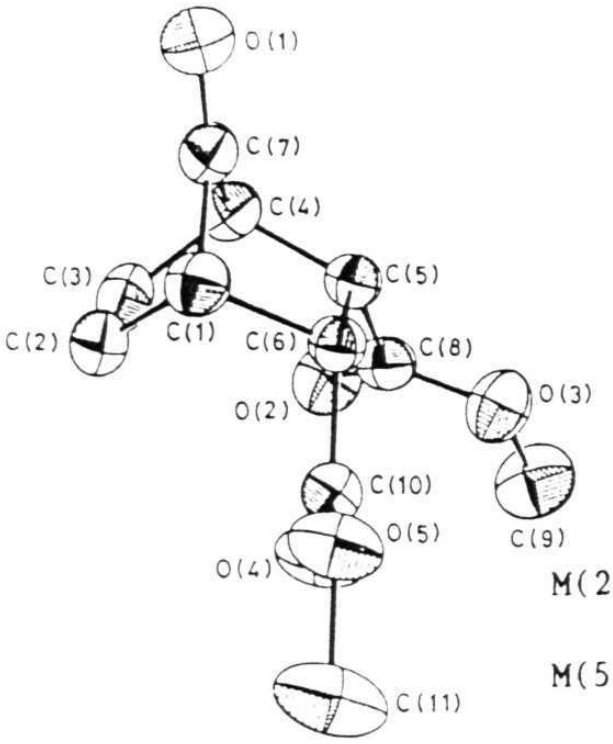
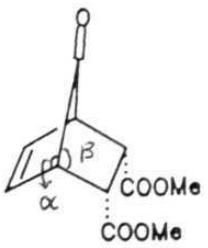
X-ray structure determination was carried out by Prof.K.Venkatesan and V. Amarendra Kumar of IISc., Bangalore.

Fig.VIII. ORTEP plot of a single molecule of 91a. Thermal ellipsoids are shown at 50% probablity levels. Bond lengths are given in A°, angles in degrees.



Parameter	X-ray(MNDO)
C(1)-C(2)	1.506(1.528)
C(2)-C(3)	1.332(1.359)
C(3)-C(4)	1.502(1.528)
C(4)-C(5)	1.551(1.579)
C(5)-C(6)	1.562(1.586)
C(1)-C(6)	1.573(1.577)
C(1)-C(7)	1.531(1.561)
C(4)-C(7)	1.532(1.560)
C(7)-O(1)	1.193(1.209)
C(8)...O(4)	2.699(3.051)
C(1)-C(2)-C(3)	108.0(110.8)
C(2)-C(3)-C(4)	109.2(110.0)
C(4)-C(5)-C(6)	104.2(103.3)
C(5)-C(6)-C(1)	102.7(103.0)
C(1)-C(7)-C(4)	96.9(95.2)
C(1)-C(7)-O(1)	131.2(132.3)
C(4)-C(7)-O(1)	131.9(132.4)
M(2,3)-M(1,4)-C(7) (α)	125.4(123.7)
M(5,6)-M(1,4)-C(7) (β)	119.2(119.1)

corresponds to the opposite stereoisomer. This result demonstrates the unimportance of ground state geometric effects in determining the π-facial selectivity in these systems.

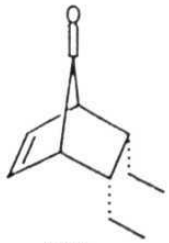


99

α=125.4°

β=119.2°

α-β=6.2°



100

MO calculations[#] using MNDO optimized geometries on 91a and related 7-norbornenone derivatives were performed. The MNDO optimized geometries correctly reproduce the structural features of interest in 91a (Fig.VIII, values in parenthesis). Interestingly, the tilt of the bridge is computed to be in the same direction for all the derivatives examined (parent 87:3.4°; 91a 4.6°; 100 4.0°). Similar magnitude of distortion, ranging from 3° to 7° was found in the two derivatives whose structures have been determined earlier. Therefore, the observed tilt of the keto bridge in 91a is not a consequence of the endo-substituents but the intrinsic preference in norbornenone systems.

A simple computational model using a test nucleophile and a test negative charge which incorporate orbital and electrostatic effects, respectively, revealed that the π-facial selectivity in 7-norbornenones can be adequately described only by effectively taking into account hyperconjugative orbital interactions involving the newly formed C-Nu σ and σ^{*} orbitals, although electrostatic interactions in the transition states also contribute.[61] Ground state geometric effects which have been postulated to operate in the parent ketone 87, are swamped by the electronic contributions from the endo-substituents.[56]

[#] MO calculations were performed in collaboration with Prof. J. Chandrasekhar and B. Ganguly of I.I.Sc., Bangalore.

II.4 endo-MONO-SUBSTITUTED-7-NORBORNANONES AND 7-NORBORNENONES:

It was considered interesting to find out whether a single substituent is enough to induce the selectivity in norbornyl systems. This study on monosubstituted norbornyl systems would also reveal the quantum of selectivity induced by a given single substituent. It would also be interesting to find out whether the face selectivity observed with two similar or different substituents is just an algebraic sum of selectivities of the each individual substituent.

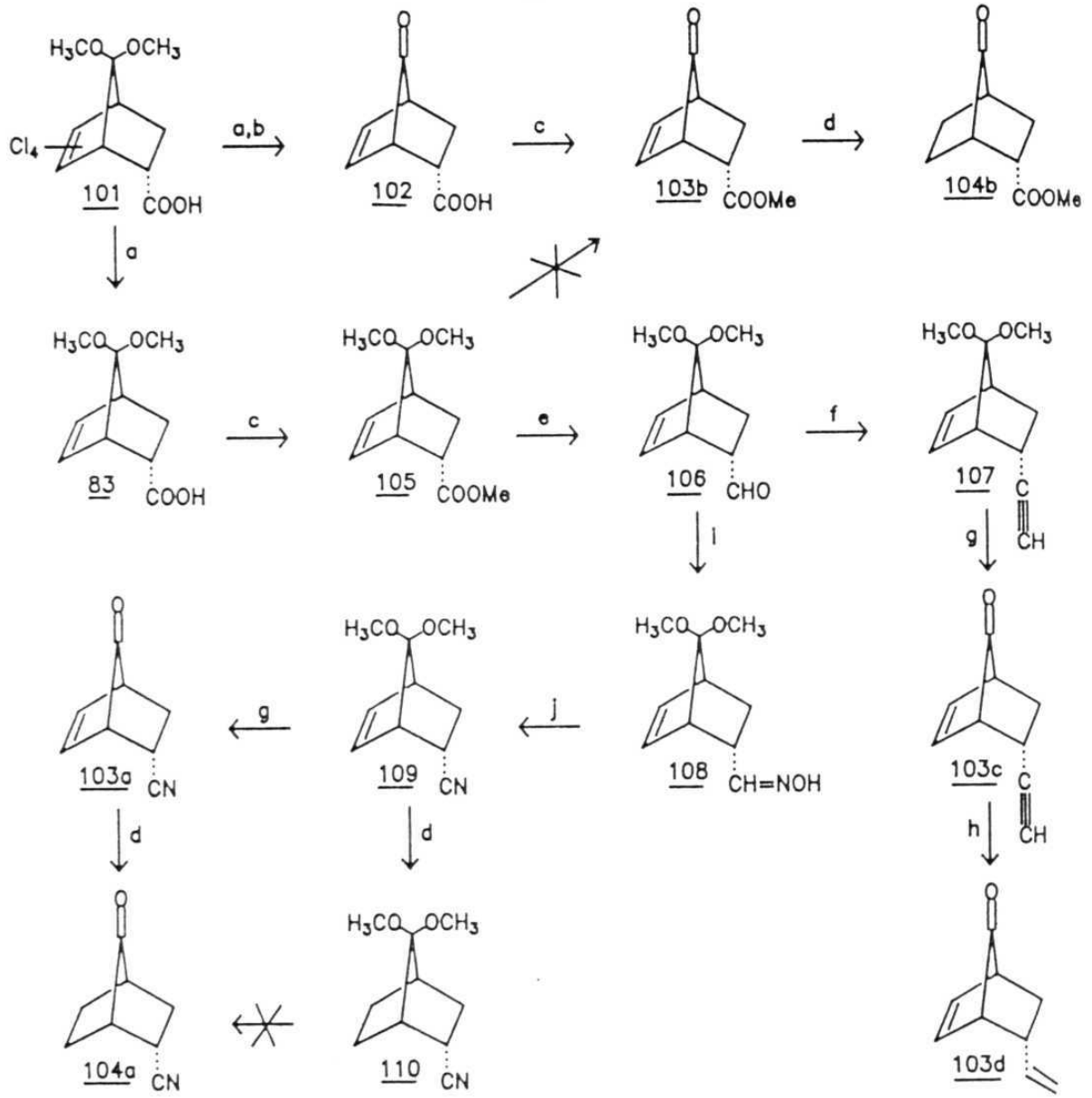
There was also a need to study systems with 'linear substituents' to rule out apprehensions that the 'bent substituents' might in some way influence the approaching nucleophiles. This is particularly important in 7-norbornenone systems in which through space interaction of lone pair of electrons of the substituents with norbornene double bond may be invoked to explain the alteration in face selectivities. Houk has recently reported[45] *ab initio* MO calculations on the 7-norbornanone derivatives with substituents such as CH_2OH and vinyl and shown that even though weakly electron withdrawing, they induce *anti*-preference through electrostatic repulsions in the *syn* transition structure between the nucleophile and the electronegative OH or vinyl group. He also reported the dependence of the calculated stereoselectivities upon the conformation of the substituents. The electrostatic repulsion of the kind described above can be minimized with linear 'look-down' substituents.

The question of more stable conformation is important only for bent substituents which can give rise to various conformations because of the free rotation of the σ bond linking the substituent with the norbornyl skeleton. Such conformations by virtue of free rotation of σ bonds are not possible with symmetrical linear substituents. It occurred to us that -C≡N and -C≡CH groups would serve as excellent linear substituents which could be easily obtained by classical methods of functional group transformations of known norbornyl derivatives.

Synthesis of monosubstituted norbornyl derivatives:

Diels-Alder adduct 101 of dimethoxytetrachlorocyclopentadiene and acrylic acid[59] served as the readily available starting material for various monosubstituted derivatives. Scheme 13 shows the synthesis of a series of monosubstituted derivatives by means of routine chemical transformations. The acid 101 on reductive dehalogenation according to literature procedure,[46] followed by warming of acidified aqueous layer prior to the extraction with organic solvent furnished keto acid 102.[46b] Esterification of 102 with diazomethane afforded keto ester 103b in 70% yield. The methyl singlet of ester group appeared at δ 3.57 in the ^{1}H NMR spectrum and the ^{13}C NMR spectrum showed 9 signals with carbonyl resonances of ketone and ester groups at δ 201.89 and 172.83, respectively. Catalytic hydrogenation of 103b using Pd/C furnished saturated ketone 104b. Several attempts to prepare 103b from the corresponding ketal 105 by

SCHEME 13



Reagents: a) Na-liq.NH_3, THF, NH_4Cl; b) 20% HCl, 60-70°C, 30 min.; c) CH_2N_2, Ether, 20 min; d) H_2, Pd/C, EtOAc; e) DIBAL-H, CH_2Cl_2, -78°C, 45 min., f) $Ph_3PCH_2Br_2$, KOt-Bu, THF, -78°C to r.t.; g) Amberlyst-15, aq.acetone, reflux, 3h; h) H_2, Lindlar Catalyst, EtOAc, 20 min.; i) $NH_2OH.HCl$, pyridine, CH_2Cl_2, r.t., 30 min., j) TsCl, pyridine, CH_2Cl_2, r.t., 4-5h.

hydrolysis using a variety of reagents and conditions failed due to the facile hydrolysis of the ester functionality under such conditions.

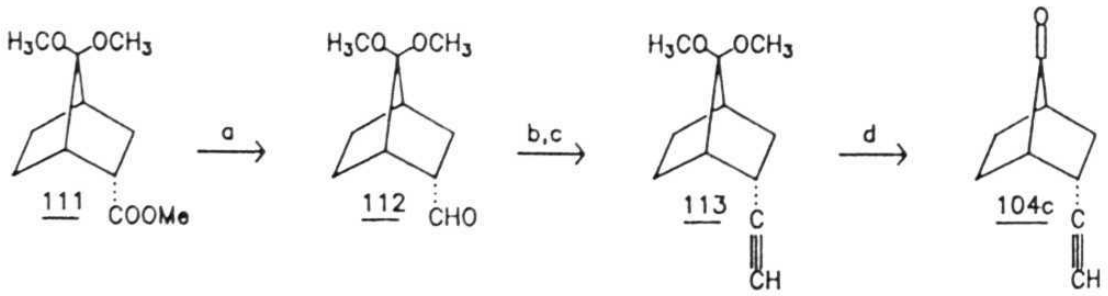
Diazomethane esterification of acid 83 following the literature procedure[46c] furnished ester ketal 105. Dibal-H reduction of 105 at -78°C furnished aldehyde 106, which is a common intermediate for the cyano and acetylene derivatives. Bromomethylene Wittig olefination[60] of 106 using *in situ* generated $Ph_3P=CHBr$ ylide followed by dehydrobromination under the basic conditions of Wittig reaction in the same pot[60] furnished acetylenic derivative 107. A doublet (J=2Hz) corresponding to the acetylenic proton at δ 1.89 and two sp-carbon signals at δ 87.59 and 67.53 in a 11 line ^{13}C spectrum supported the structure 107. Ketone 103c was obtained in 73% yield by the acid catalyzed hydrolysis of 107. The acetylenic proton in 103c appeared at δ 1.98 and the ^{13}C NMR had 9 lines with carbonyl carbon peak at δ 202.72. Chemoselective hydrogenation of 103c using Lindlar catalyst furnished vinyl derivative 103d which showed 1770 cm^{-1} peak in the IR spectrum and vinyl proton signals in the ^1H NMR spectrum at δ 5.84-5.28 and 5.14-4.86 in a ratio of 1:2.

Aldehyde 106 upon treatment with $NH_2OH.HCl$ and pyridine gave a mixture of cis and trans-oximes 108. Dehydration of oximes was achieved by reaction with TsCl and pyridine to give cyano derivative 109 in 65% yield. The IR spectrum

showed diagnostic peak at 2230 cm^{-1} and the ^{13}C NMR spectrum showed 10 lines with cyano group carbon peak at δ 122.48. Amberlyst resin catalyzed hydrolysis gave ketone 103a in 60% yield. Catalytic hydrogenation of 103a furnished the saturated ketone 104a, which showed peaks at 2230, 1770 cm^{-1} in the IR spectrum and δ 210.89, 120.55 peaks in the ^{13}C NMR spectrum. The ketone 104a exhibited a very high tendency to form hydrate on storage. It was not possible to obtain 104a via the saturated ketal 110, as all attempts to hydrolyze it failed.

Scheme 14 describes the preparation of 104c. Ester 111, which was obtained by the hydrogenation of the corresponding unsaturated derivative, gave aldehyde 112 upon DIBAL-H reduction at -78°C. Aldehyde 112 upon Wittig olefination using $Ph_3P{=}CHCl$ gave a haloalkene which on further treatment with potassium tert-butoxide furnished the acetylenic derivative 113. The acetylenic carbons appeared at δ 87.35 and 69.29 in the ^{13}C NMR spectrum. Amberlyst

SCHEME 14



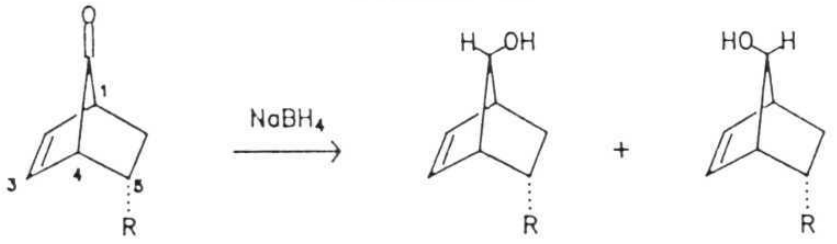
Reagents: a) DIBAL-H, CH_2Cl_2, -78°C, 45 min.; b) Ph_3PCH_2ClBr, KOt-Bu, THF, -78°C to r.t., 1.5h; c) KOt-Bu, THF, r.t., 12h; d) Amberlyst-15, aq.acetone, reflux, 10-12h.

catalyzed hydrolysis of 113 gave the ketone 104c in 51% yield with carbonyl resonance at δ 214.53 and acetylenic carbons at δ 85.06, 70.77.

$NaBH_4$ reduction of ketones 103a-d and 104a-c:

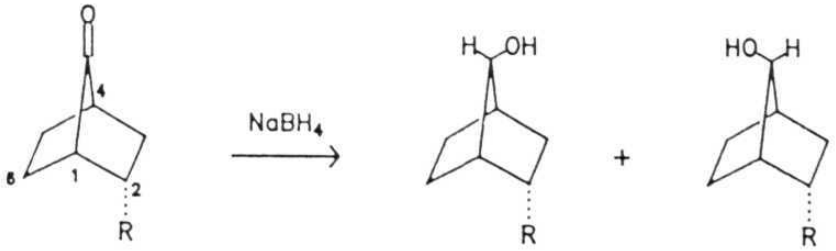
The $NaBH_4$ reduction of both saturated and unsaturated ketones[61] 103a-d and 104a-c furnished a mixture of diastereomeric alcohols 114a-d, 115a-d and 116a-c, 117a-c in each case (Scheme 15, 16). The product distribution was obtained from the ^1H NMR integration of the crude reaction

Scheme 15



103a	R=C≡N	114a	44 : 56		115a
103b	R=COOMe	114b	68 : 32		115b
103c	R=C≡CH	114c	72 : 28		115c
103d	R=Vinyl	114d	>90 :	traces	115d

Scheme 16



104a	R=C≡N	116a	12 : 88		117a
104b	R=COOMe	116b	32 : 68		117b
104c	R=C≡CH	116c	31 : 69		117c

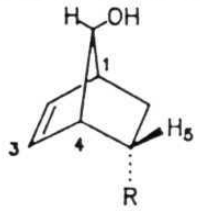
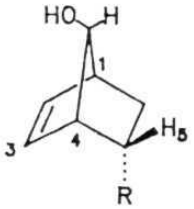
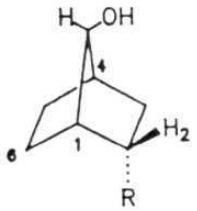
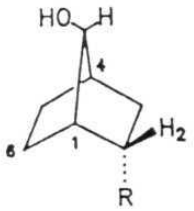
mixture. The isomeric mixture of alcohols were separated in all the cases and fully characterized. The observed face-selectivities in hydride reduction are shown in Schemes 15 & 16.

Stereochemical assignments:

The stereochemical assignments are again based on the greater deshielding of C_5-exo proton in 7-norbornenone series and C_2-exo proton in 7-norbornanone series of syn-alcohols compared to the same protons in the anti-alcohols, Table 8 (also see, Figs.25-35 in Section V). Similarly, the well separated olefinic protons experience downfield shift in anti-7-norbornenols 115a-d (OH group on the side of the double bond) compared to the olefinic protons of syn-norbornenols 114a-d.# All the unsaturated alcohols were individually hydrogenated and compared with the $NaBH_4$ reduction products of saturated ketones 104a-c. In the case of vinyl derivative 103d, the ^1H NMR of crude $NaBH_4$ reaction mixture did not show peaks corresponding to anti-115d. The stereochemistry of the exclusive product 114d was supported by chemical shift value of its exo-H_5 (δ 3.12-2.80) and unambiguously confirmed by hydrogenation to the syn-alcohol of acetylene derivative 114c using Lindlar catalyst.

For the sake of uniformity with the results on saturated 7-norbornanones 104a-c, syn and anti prefixes are used with reference to endo-substituent.

Table 8. ^1H NMR resonances of H_5 and H_2 in <u>syn-</u> & <u>anti</u>-7-norbornenols and 7-norbornanols, respctively.

	 H_5	 H_5
1. R=CN	δ 3.12	δ 3.02-2.80
2. R=COOMe	3.20	3.06-2.76
3. R=C≡CH	3.18-2.92	2.94-2.72
	 H_2	 H_2
1. R=CN	δ 3.30-3.02	δ 2.88-2.60
2. R=COOMe	3.33-3.05	2.88-2.60
3. R=C≡CH	3.24-2.98	2.73-2.60

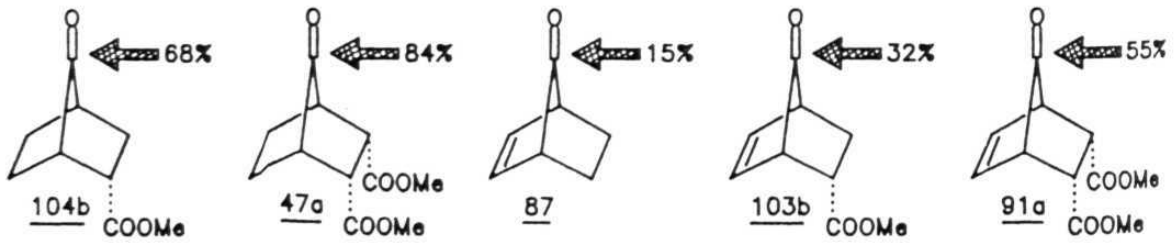
Interpretation of results:

The results clearly show that even a single <u>endo</u>-substituent in norbornyl systems is capable of inducing significant face-selectivity. The linear 'look-down' substituents, which are electron withdrawing in nature (-C≡N, -C≡CH), do confer <u>syn</u>-preference (approach from the substituent side) on the approaching nucleophiles similar to their 'bent' counterpart (-COOMe). Vinyl group in <u>103d</u> induces

small anti-preference (approach from the double bond side) compared to parent and thus behaves like a donor group. The -C≡CH group is behaving normally as an electron withdrawing group unlike the 'free rotating' vinyl group whose abnormal behavior was rationalized[42] (vide supra) in terms of through space electron donation from the π-lobes in a perpendicular conformation. Such participation of π-electrons either does not seem to be operating in the case of -C≡CH group or may be over-ridden by the increased electronegativity of sp-carbon of -C≡CH compared to sp^2 carbon of vinyl group.

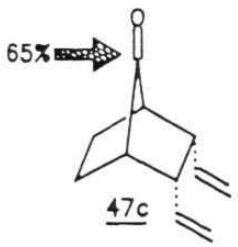
Another noteworthy feature is the additive impact of the substituents. Consider the mono and disubstituted ester derivatives 104b, 47a, 103b and 91a in both saturated and unsaturated series (see Scheme 17). A single ester substituent in 104b is inducing syn-attack to the extent of 68% and the rest is anti-attack. That means the effective

Scheme 17

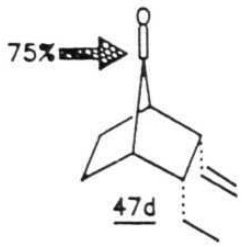


magnitude of syn-preference induced by an ester group is 18%. This on extrapolation would mean that the effective magnitude of syn-preference for two ester groups would be 36% (18% + 18%). This is indeed observed in practice for 47a with two ester groups which shows 34% effective magnitude of syn-preference. Similarly, in 7-norbornenone

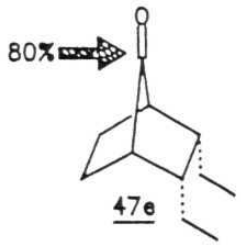
series, the effective magnitude of syn-preference induced by one ester group in 103b is 17% and two ester groups in 91a is 40% when compared to the parent ketone 87. This result indicates that the contribution to face-selectivity from the two endo-substituents is simply the algebraic sum of the contributions due to each group. This cumulative effect may be conveniently used to predict face-selectivity in some of the disubstituted norbornyl systems which have not been studied so far because of difficulties involved in their preparation. The effectiveness of this rule is also exemplified by the following set of results, discussed previously. The magnitude of effective contribution for each



47c



47d



47e

vinyl group in 47c is 7.5% and for each ethyl group in 47e is 15%. The algebraic sum of the contributions of two groups is 22.5%, which is close to what is actually found for 47d (25%) with one ethyl and one vinyl substituents.

II.5 endo-MONO- AND endo, endo-DISUBSTITUTED BICYCLO[2.2.2]-OCTANONES:#

Is the observed face selectivity an inherent characte-

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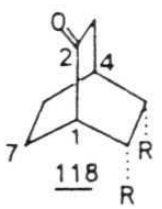
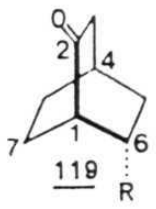
endo-prefix refer to the substituent being below the C_5, C_6, C_7, C_8 plane and on the blind side of the carbonyl group.

ristic of the norbornyl systems? To answer this question and to extend our initial observations on "remote substituent guided face selectivity" in norbornyl systems, we also ventured to study the endo, endo-disubstituted bicyclo-[2.2.2]octanone 118 and endo-mono-substituted bicyclo-[2.2.2]octanones 119, 120. The steric neutrality and conformational rigidity present in norbornyl system is retained in these systems too. However, unlike in norbornyl systems, two regioisomeric mono endo-substituted derivatives are possible for a given substituent in these systems. This built-in difference makes monosubstituted derivatives a novel probe to unravel some of the interesting aspects of orbital and electrostatic components. Electronic effects comprises of these two components (orbital and electrostatic) which are extremely difficult to segregate in experimental probes. In the probe systems experimentally studied

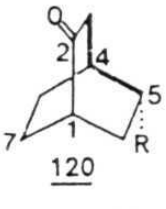


118



119

'ON' position



120

'OFF' position

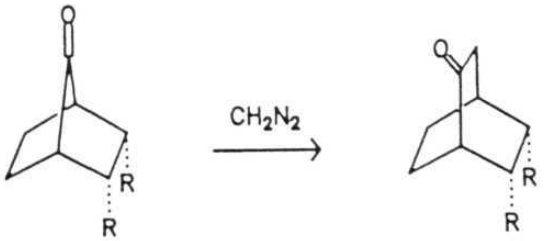
so far by us, the emphasis was to segregate steric effects from electronic effects. Further segregation of electronic effects into its components was not possible in the earlier studies. But the unique skeleton of bicyclo[2.2.2]octanones provides an opportunity to distinguish between the two components by virtue of its existence as two regioisomers of monosubstituted derivatives. This important feature, unlike

in norbornyl system, renders additional advantage of keeping a substituent at the "ON" (such as 119) or "OFF" (such as 120) position with respect to the orbital interactions and hence offers an opportunity to test the validity of Cieplak model in these systems.

Synthesis of endo-bicyclo[2.2.2]octanone derivatives:

5,6-endo,endo-Disubstituted bicyclo[2.2.2]octanones 118a-c,e are not easy to access synthetically as the Diels-Alder methodology employed for constructing bicyclo[2.2.2]-octane systems does not provide the requisite functionalization and stereochemistry. The endo, endo-disubstituted-bicyclo[2.2.2]octanones were therefore prepared from the corresponding 7-norbornanones 47a-c,e via diazomethane mediated ring expansion protocol, Scheme 18. Reasonable yields were obtained in each case. All the ketones 118a-c,e showed satisfactory ^{1}H and ^{13}C NMR spectral characteristics. The number of signals in the ^{13}C NMR spectra doubled in going from starting 7-norbornenones (6 lines) to

SCHEME 18



47a R=COOMe

47b R=CH_2OMe

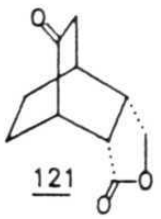
47c R=Vinyl

47e R=Ethyl

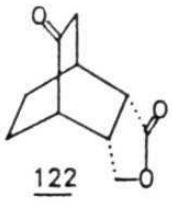
118a-c,e

bicyclo[2.2.2]octanones (12 lines) because of the loss of symmetry on one carbon ring expansion. The endo stereochemistry of the products 118a-c,e was secured by the analyses of ^{13}C NMR data in which C_7 and C_8 resonances are shielded by the C_5 and C_6 endo substituents in the same manner as in 7-norbornanones 47a-c,e.

The two regioisomers of the monosubstituted ester ketone 119b and 120b (R=COOMe) were prepared by the diazomethane mediated one carbon ring expansion of the corresponding monosubstituted 7-norbornanone ester 104b. The regioisomeric lactones 121 and 122, which are synthetically useful cyclic anlogues of monoester derivatives 119b and 120b, were also prepared from corresponding lactone derivative of 7-norbornanone 133, described later in the sequel (Scheme 20). The details of the ring expansion reactions of these monosubstituted norbornanone derivatives and the regiochemistry of the products will be discussed under separate heading (Section II.6).



121



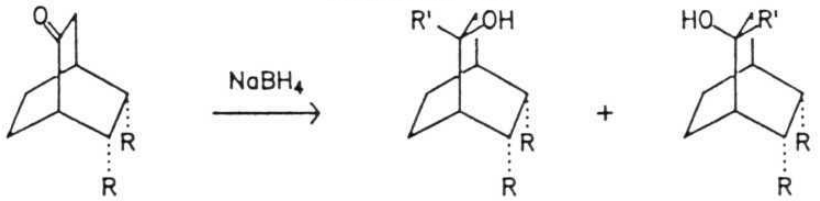
122

$NaBH_4$ reduction and methyllithium addition to bicyclo-[2.2.2]octanones:

The ketones 118a-c,e were subjected to hydride reduction with $NaBH_4$ and DIBAL-H and methylation with methyl lithium to furnish syn-123a-c,e and anti-124a-c,e alcohols[62]

(Scheme 19) in near quantitative yield. The ratios of syn : anti products are summarized in Table 9. The diastereomeric mixture of alcohols were separated in all the cases by means of column chromatography. In the case of the

SCHEME 19



118a R=COOMe 123a R_1=H 124a R_1=H

118b R=CH_2OMe 123b R_1=H 124b R_1=H

118c R=Vinyl 123c R_1=H,Me 124c R_1=H,Me

118e R=Ethyl 123e R_1=H,Me 124e R_1=H,Me

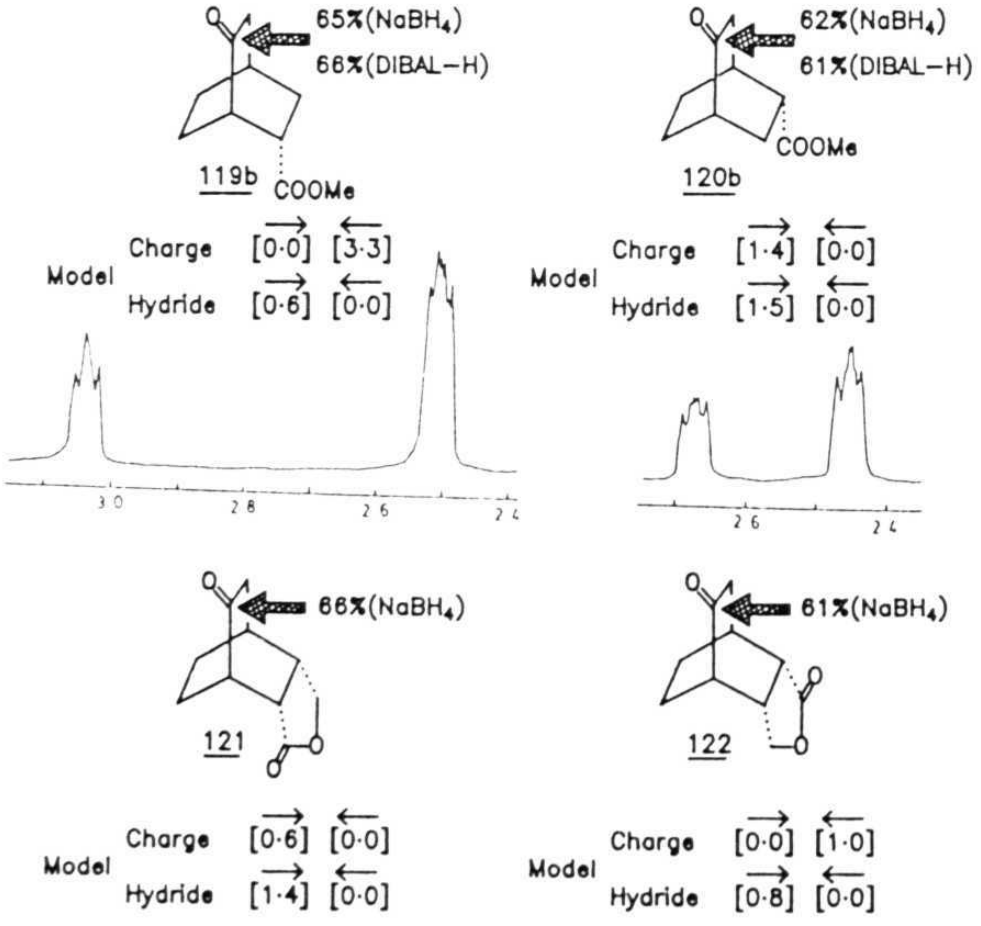
Table 9. Product ratios in the metal hydride reduction and methyllithium additions to 118a-c,e.

	syn : anti ratio		
Substrate	$NaBH_4$	i-Bu_2AlH	MeLi
118a	30 : 70	33 : 67	----
	(123a) (124a)	(123a) (124a)	
118b	48 : 52	----	----
	(123b) (124b)		
118c	50 : 50	50 : 50	46 : 54
	(123c) (124c)	(123c) (124c)	(123c,R_1=Me)(124c,R_1=Me)
118e	61 : 39	65 : 35	66 : 34
	(123e) (124e)	(123e) (124e)	(123e,R_1=Me)(124e,R_1=Me)

mixture of alcohols derived from dimethoxy derivative 118b in which the two isomers were not resolving on tlc plate the separation was achieved by converting them into the corresponding acetates and separating the individual diastereomeric acetates by means of column chromatography. The individual acetates on hydrolysis with methanolic KOH furnished the pure alcohols 123b and 124b in quantitative yield.

The results of $NaBH_4$ and DIBAL-H reductions[62] of regioisomeric monosubstituted ketones 119b and 120b are shown on the structures in Fig.IX. The lactones 121 and 122, which are cyclic analogues of monoester derivatives 119b and 120b, also show similar selectivity during $NaBH_4$ reduction as

Fig.IX

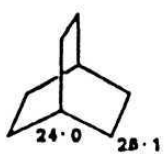


shown on the respective structures, Fig.IX. The nucleophiles approach preferentially from the syn-face in both the pairs (119b, 120b and 121, 122) of regioisomers. The peaks corresponding to substituent attached methine protons of syn- and anti-alcohols in the ^1H NMR spectra of the crude reduction products from 119b and 120b which were used for calculating the product ratios, are also shown in Fig.IX.

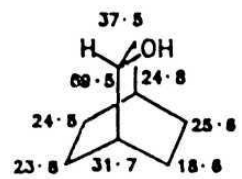
Stereochemistry of syn- and anti-alcohols:

The stereostructures of 123a-c,e and 124a-c,e and the alcohols derived from 119b, 120b as well as 121, 122 have been unambiguously assigned on the basis of analyses of both the ^1H and ^{13}C NMR data. The relative deshielding (0.3 ppm) of the exo-6H proton in syn-alcohols 123a-c,e compared to anti-alcohols 124a-c,e in the ^1H NMR spectra is similar to that observed in norbornyl systems (see, Figs.36-39). The stereochemical assignments to products derived from 119b, 120b, 121 and 122 were also based on similar trend (see Fig.IX).

In bicyclo[2.2.2]octanols, the ^{13}C spectra are also of diagnostic value due to shielding effect induced by the hydroxyl group on the syn-transannular carbon resonance. It is well known that γ-OH group in bicyclo[2.2.2]octan-2-ols exerts shielding effect on C_6 resonance (compare 125 and 126).[63] The shielding of C_6-resonances in syn-alcohols and



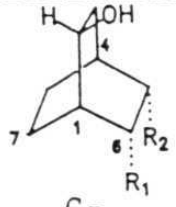
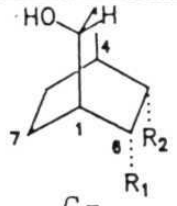
125



126

C_7 in the anti-alcohols by about 4-6 ppm is a convenient tool to further confirm the stereochemical assignments. Table 10 lists the the chemical shift values (in ppm) for C_7 resonances of syn-123a-c,e and anti-124a-c,e as well as for the syn and anti products derived from 119b and 120b.

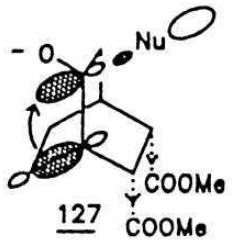
Table 10. ^{13}C NMR resonances of C_7 in endo-substituted bicyclo[2.2.2]octan-2-ols.

		 C_7	 C_7
1.	R_1=R_2=COOMe	δ 20.11	δ 14.23
2.	R_1=R_2=CH_2OMe	19.23	13.88
3.	R_1=R_2=Vinyl	19.47	14.11
4.	R_1=R_2=Ethyl	18.82	13.58
5.	R_1=COOMe, R_2=H	19.70	14.76
6.	R_1=H, R_2=COOMe	20.29	17.76

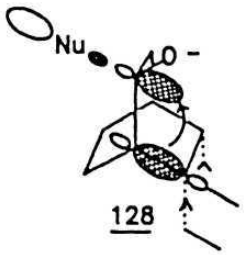
Interpretation of results:

The data in Table 9 clearly indicates that the remote endo-substituents have a profound bearing on the face-selectivity in nucleophilic additions to 118a-c,e. The electron withdrawing ester substituents in 118a induce syn-preference whereas in the case of 118e having electron donating alkyl substituents the selectivity is reversed and anti-approach is preferred. On the other hand, the endo-substituents like

methoxymethyl (118b) and vinyl (118c), with relatively modest inductive contribution, exhibit no facial bias in the metal hydride reductions. The vinyl derivative 118c shows slight syn-preference (54 : 46) during addition of methyl lithium. The selectivities induced by the endo-substituents in these systems are generally consistent with those obtained for the norbornyl derivatives 47a-e, and can be reconciled in terms of the Cieplak model.[13] Thus, for 118a, with electron withdrawing substituents, hyperconjugation from the more electron rich C_1-C_7 σ bond favors the syn-approach of the nucleophile, as shown in 127. On the same basis, the donor groups in 118e lead to preferential addition to the anti-face, as shown in 128.



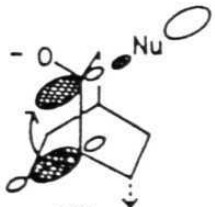
127



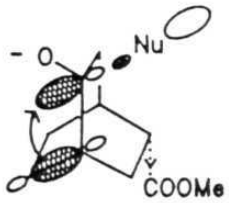
128

The results of metal hydride reduction of regioisomeric pairs of ketones 119b, 120b and 121, 122 are rather surprising at first sight. Application of Cieplak's hyperconjugative model[13] leads to the prediction of preferential syn-face addition for the ketone 119b, as shown in 129, and no facial preference in the regioisomeric ketone 120b, as neither of the two vicinal (C_1-C_6 and C_1-C_7) σ bonds is perturbed by the C_5-substituent (see 130 and 131). A similar argument holds good for the regioisomeric pair of lactones 121 and 122. However, as is visually obvious from

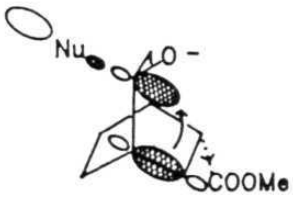
the peak areas in Fig.IX, both 119b and 120b exhibit a moderate syn-preference when subjected to $NaBH_4$ and DIBAL-H reduction. The regioisomeric pair of lactones 121 and 122 also exhibited similar selectivity during $NaBH_4$ and DIBAL-H reduction, Fig.IX. Thus, there is little difference in the face selectivity whether the endo substituent is at the "ON" or the "OFF" position for orbital interactions.



129



130



131

To unravel the origin of the observed face-selectivities in monosubstituted ester derivatives 119b and 120b, a simple computational model[#] in which the geometries of the substrates were optimized at MNDO level was employed. To probe the role of electrostatic effects, a test negative charge was placed above the carbonyl carbon atom orthogonal to the π-plane, at a typical interaction distance of 1.4 A. The computed energy difference with charge on either face of the carbonyl group would then indicate the preference induced by electrostatic effects. A similar calculation with a test nucleophile (H^-) leads to a prediction which effectively incorporates orbital interactions also.

[#] MO calculations were performed in collaboration with Prof. J. Chandrasekhar and B. Ganguly of IISc., Bangalore.

Calculated relative energies (Kcal/mol) between syn and anti approach to 119b and 120b using charge and hydride models[61] are shown below on the respective structures in Fig.IX. A point negative charge placed at the syn face of the carbonyl unit in 119b is computed to be less favorable than the alternative anti face approach by 3.3 Kcal mol^{-1}. However, in the hydride model, the preference is reversed making the syn-face interaction more attractive by 0.6 Kcal mol^{-1}, in agreement with experimental product ratios. Thus, hyperconjugative interactions involving the electron rich C_1-C_7 σ bond have to overcome unfavorable electrostatic interactions to effect the observed face selectivity. In 120b, the electrostatic contribution favors the syn-face attack (1.4 K cal mol^{-1}). Use of hydride ion as a probe yields essentially the same energy preference, confirming the absence of face-selective hyperconjugative interactions in this system. Overall, the selectivity remains similar to that observed for 119b.

The computed charge distributions provide a clue to the reversal of the electrostatic preference for 119b and 120b. The ester group produces significant positive charges at C_5, C_6 and the exo hydrogen atoms in both 119b and 120b, leading to favorable interaction with a negative charge near syn-face. However, a large build-up of negative charge on the ester oxygen atoms leads to considerable repulsion in 119b relative to 120b.

II.6. APPENDIX: OBSERVATION OF LONG-RANGE SUBSTITUENT EFFECTS ON THE REGIOSELECTIVITY OF ONE-CARBON RING EXPANSION OF 7-NORBORNANONES

Diazomethane is frequently employed for one-carbon ring expansion of mono- and poly-cyclic ketones and is a valuable synthetic manoeuvre for gaining entry into higher homologues.[64] The regioselectivity in this transformation is not always predictable and exhibits marked dependence on the nature of the substrate and particularly on the substituents flanking the carbonyl group.[64c,e,f]

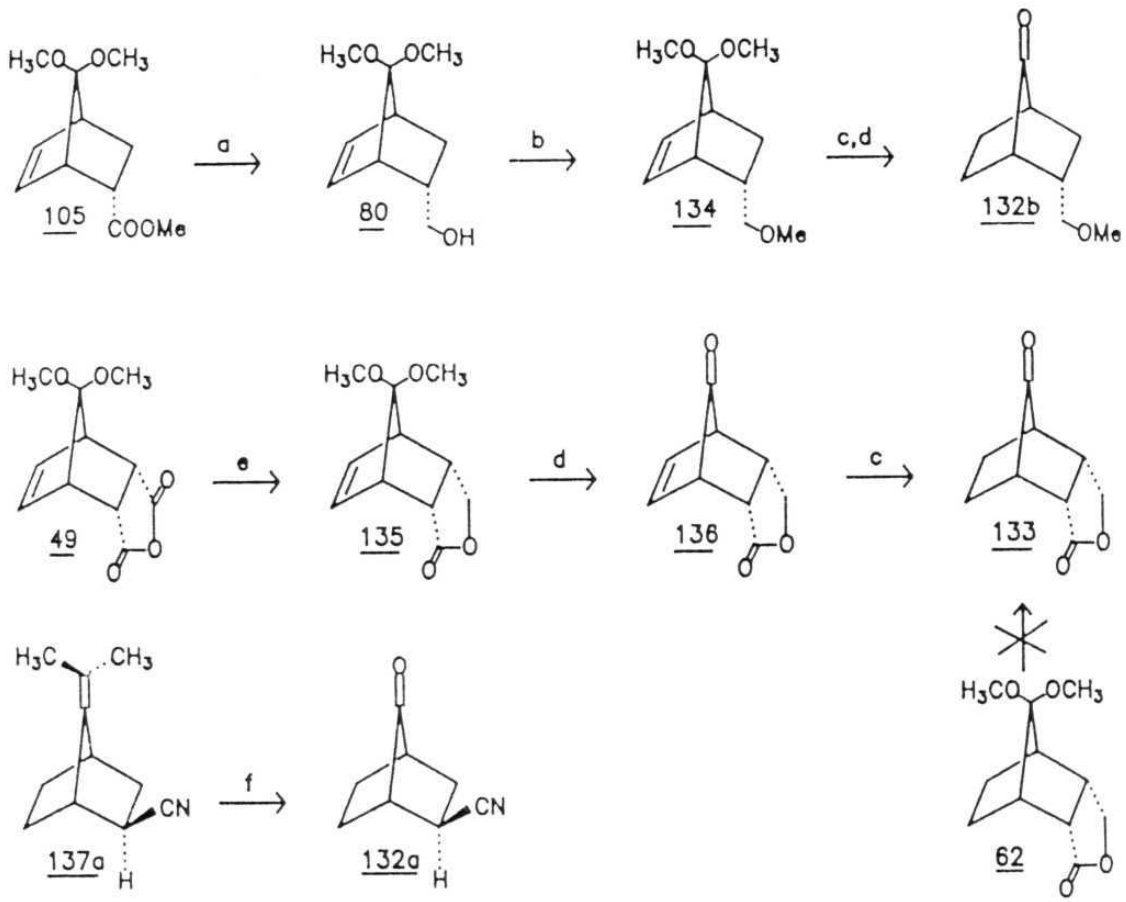
Diazomethane mediated one carbon ring expansion of 2-substituted-7-norbornanones was considered as a convenient route to the monosubstituted bicyclo[2.2.2]octanones which are otherwise difficult to prepare by other methods. The latter compounds were required in connection with π-facial selectivity studies to serve as important probe systems[62] to evaluate orbital and electrostatic components (see previous section). One carbon ring expansion of unsymmetrical monosubstituted norbornanones would lead to two regioisomers corresponding to the migration of front bond 'a' and back bond 'b' (see Scheme 21). If the migratory aptitudes of these two bonds are different then the ring expansion would result in the formation of unequal amounts of the regioisomers. Of the two bonds, the one which is relatively electron rich would migrate in preference to the other apparently equivalent bond. This in turn depends upon the

inductive influence of the β-substituent on the bond 'a' through an intervening C_1-C_2 σ bond. There is only one literature report so far of 7-norbornanone ring expansion to give bicyclo[2.2.2]octan-2-one and it does not involve any regiochemical issues.[65]

Synthesis of monosubstituted 7-norbornanones:

The synthesis of 2-substituted 7-norbornanones 104a,b was discussed earlier, Scheme 13. The ketones 132a,b and 133 were synthesized as depicted in Scheme 20. O-Alkylation using NaH and MeI of the alcohol 80[46] obtained by the $LiAlH_4$ reduction of mono ester 105,[46c] followed by hydrogenation and acid catalyzed hydrolysis furnished ketone 132b. The IR spectrum of 132b showed strong carbonyl absorption at 1770 cm^{-1} and ^{13}C showed 9 signals with carbonyl resonance at δ 215.60. All attempts to hydrolyze the lactone ketal 62 to obtain the ketone 133 failed. Fortunately, the unsaturated lactone ketal 135, obtained by treatment of anhydride 49 with $NaBH_4$, underwent smooth hydrolysis to furnish unsaturated ketone 136. Hydrogenation of 136 over Pd-C at atmospheric pressure afforded ketone 133. Apearence of methylene protons of lactone ring at δ 4.53, 4.41 in the ^1H NMR spectrum and 9 line ^{13}C NMR spectrum with two carbonyl signals at δ 209.89 and 176.30 confirmed the structure. The 2-exo-cyano-7-norbornanone 132a was obtained by ozonolysis of the corresponding 7-isopropylidene derivative 137a (preparation of 137a will be described later in the sequel). Appearence of endo-H_2 at δ 2.76 (upfield shift compared to

Scheme 20



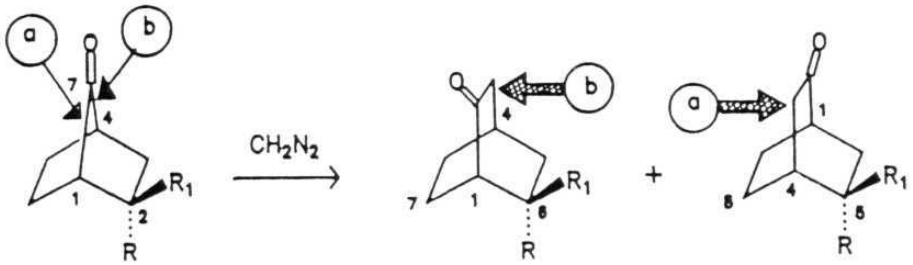
Reagents: (a) $LiAlH_4$, ether, r.t., 4-5 h ; (b) NaH, MeI, THF, r.t., 40 min ; (c) H_2, Pd-C, EtOAc, 30 min ; (d) Amberlyst-15, aq.acetone, reflux, 1.5 h ; (e) $NaBH_4$, THF, 0-5°C, 1.5 h ; (f) O_3, CH_2Cl_2, -78°C ; Me_2S, -78°C ---> r.t., 1h.

<u>exo</u>-H_2 in <u>104a</u>, δ 3.11) in the ^1H NMR spectrum and 7 line ^{13}C NMR spectrum with $C_{5,6}$ resonances appearing as a single line at δ 22.70 (these resonances appear at δ 23.29 and 19.35 respectively in the <u>endo</u>-isomer <u>104a</u>) supported the structure <u>132a</u>.

Diazomethane ring expansion of monosubstituted 7-norbornanones:

One-carbon ring expansion of 2-substituted-7-norbornanones 104a,b and 132a,b using diazomethane[66] furnished a regioisomeric mixture of bicyclo[2.2.2]octanones 119a,b, 120a,b and 138a,b, 139a,b. The results are summarized in Scheme 21. The regioisomers in each case were separated by means of column chromatography. In the case of 138a and 139a, the regioisomeric mixture of ketones were converted

Scheme 21



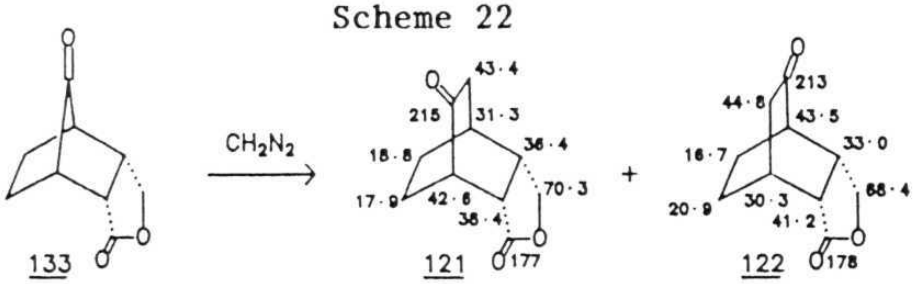
104a	R=CN, R_1=H	119a	71 :	29	120a
104b	R=COOMe, R_1=H	119b	63 :	37	120b
132a	R=H, R_1=CN	138a	61 :	39	139a
132b	R=CH_2OMe, R_1=H	138b	60 :	40	139b

into the corresponding ethylene ketals. The two isomeric ketals in the mixture resolved well on tlc plate, facilitating the column chromatographic separation of individual regioisomers. Acid catalyzed hydrolysis of the each individual ketal furnished pure ketones 138a and 139a.

The ring expansion of the 7-norbornanone based endo-lactone 133 furnished synthetically useful bicyclo[2.2.2]-

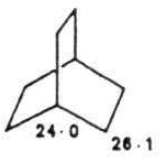
octanones 121 and 122 with 63 : 37 regioselectivity, Scheme 22. The isomers 121 and 122 did not resolve on tlc plate for direct column separation. Hence, they were first converted into a mixture of corresponding ethylene ketals and separated by column chromatography. Acid catalyzed hydrolysis of pure ketals furnished ketones 121 and 122.

Scheme 22

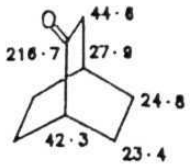


Stereochemistry of endo-monosubstituted bicyclo[2.2.2]octan-2-ones:

Structures of regioisomeric ketones 119a,b, 120a,b and 138a,b, 139a,b are based on analyses of their ^{13}C NMR data, Table 11. The ^{13}C chemical shift values of parent bicyclo-[2.2.2]octane 125 and bicyclo[2.2.2]octanone 140[63] are also shown for comparison purpose. The carbonyl group in 140 shields resonances of both the transannular β-carbons (i.e., C_6 and C_7). This effect, along with the γ-steric compression effect of endo-substituent on either C_7 or C_8, serves the diagnostic purpose of stereochemical assignments to regioisomers. Thus, the major feature of the ^{13}C spectral



125



140

assignment is that C_7 in the regioisomeric series 119a,b, 138a,b is shielded both by the C_2-carbonyl as well as the C_6-endo-substituent. By comparison, in the 120a,b, 139a,b series both C_7 and C_8 are shielded by the C_2-carbonyl and C_5 endo-substituent, respectively. Thus, C_7-C_8 ^{13}C resonances have larger separation in the 119a,b, 138a,b series than in the 120a,b, 139a,b. The shielding effect of carbonyl is also discernible in the C_5 and C_6 resonances in both the regioisomeric series. A similar analyses of the ^{13}C NMR

Table 11. ^{13}C NMR resonances of C_1-C_8 in monosubstituted bicyclo[2.2.2]octan-2-ones.

Subst.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
119a	43.70	212.18	43.53	27.17	29.82	24.61	19.29	23.70
120a	41.06	213.19	43.53	31.41	26.70	27.94	22.35	20.58
119b	43.82	214.95	44.59	27.70	27.47	38.29	19.23	24.29
120b	41.82	216.01	44.47	31.47	41.17	25.35	22.47	20.64
138a	44.59	211.24	44.17	27.11	30.12	25.70	22.47	23.06
139a	40.88	213.12	40.88	31.53	26.17	27.82	22.00	24.06
138b	43.47	216.77	43.70	27.70	28.82	31.94	17.41	24.82
139b	42.35	217.59	45.41	28.94	35.35	27.29	23.23	19.11

^{13}C NMR Spectra were recorded in $CDCl_3$. Assignments are based on internal consistency, off-resonance multiplicities in some cases and comparison with known bicyclo[2.2.2]octanones. Chemical shifts within 1-2 ppm range can be interchanged.

shieldings in exo-138a and 139a led to their formulation (see Table 11).

The structural assignments for 121 and 122 again follow from the ^{13}C NMR values depicted on their structures, Scheme 22.

Interpretation of results:

The results summarized in Scheme 21 indicate that the electron withdrawing substituents, such as CN, COOMe, at the C_2-endo position significantly diminishes the propensity of the 'a' (C_1-C_7) bond to migrate vs the 'b' (C_4-C_7) bond. The ester 104b (Scheme 21) and lactone 133 (Scheme 22) show the same selectivity in the ratio 63 : 37 in which the major product is derived from the migration of 'b' bond. The endo-CN group in 104a induces the highest selectivity among all the substrates studied (71 : 29). To rule out the possibility that the observed selectivity is due to the placement of substituents with respect to carbonyl such that the two dipoles oppose each other, an experiment with exo-CN derivative 132a was carried out. The results in Scheme 21 demonstrate that even the C_2-exo cyano group in 132a induces a similar migratory preference to furnish 138a (61 : 39) and 139a. Thus, the electronic effect of the C_2-substituent is operative in the ring expansion irrespective of its stereochemistry. While the inductive effect of the α-substituents on the regioselectivity in diazomethane ring expansions is quite well precedented, this, to our knowledge, is

the first example of a significant effect of the remote β-substituent on the regioselectivity of ring expansion.

Also, the above results have some bearing on the interpretation of the origin of face-selectivities in nucleophilic additions to endo-substituted 7-norbornanones. The predominant syn-selectivity observed for additions to 7-norbornanones 104a-c could be ascribed to co-operative or competitive influences of orbital and electrostatic effects. Cieplak model which is based on orbital effects, emphasizes the importance of transition state stabilization involving electron rich anti-periplanar σ bond and antibonding σ^* orbital of the incipient C-Nu bond. This interpretation requires that C_1-C_2 bond in 104a-c be electron deficient compared to the C_1-C_6 bond as well as the C_3-C_4 and C_4-C_5 bonds. The above results indicate that this is indeed so, in the ground state, as the C_2-substituent effect is felt even further in rendering the C_1-C_7 bond electron deficient compared with C_4-C_7 bond which exhibits preferred migratory aptitude in the ring expansion.

SECTION B: ELECTROPHILIC ADDITIONS TO NORBORNYL SYSTEMS:

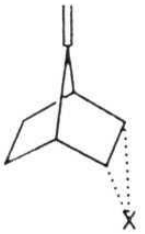
II.7 2,3-endo, endo-DISUBSTITUTED-7-METHYLENENORBORNANES:

Electrophilic additions are complementary to the nucleophilic additions in the sense that the reagent contributes the bonding pair of electrons to trigonal carbon atom in the latter whereas it is just the reverse in the case of former. Further, the frontier molecular orbitals of substrate and reagent interacting with each other are reversed in the two types of additions, e.g., HOMO of nucleophile interacts with LUMO of carbonyl in nucleophilic additions and LUMO of electrophile interacts with HOMO of the olefin in the case of electrophilic additions.

Klein in his model[11] to explain the selectivities in cyclohexane based systems pointed out that the unsymmetrical extension of π and π^* orbitals due to interaction with unoccupied and occupied β C-C bonds respectively are responsible for facial discrimination. Based on different electron density on the two faces of the plane containing trigonal atom, he predicted that the electrophilic attack involves preferential equatorial approach by interaction with π orbital, but nucleophilic attack involves preferential axial approach by interaction with π^* orbital. Recently, Reetz and co-workers[67] using ab initio MO calculations refuted the above argument and showed that unsymmetrical extension of the orbitals is in the same direction for both π and π^*, with π HOMO and π^* LUMO larger on the axial face. Application of Cieplak's hyperconjugative

model[13] predicts that irrespective of which reacting partner contributes the bonding electrons, the directional preference should remain same and from the side opposite to most electron rich anti periplanar σ bonds.

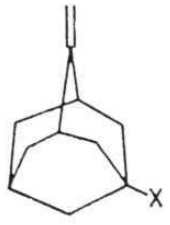
The vast majority of the experimental results available in the literature are on cyclohexane based systems[13,27,68] which make the issue further complicated because of the presence of several competing factors in these systems. Little attention has been paid to control the electrophilic stereoselections through remote electronic influences in sterically neutral situations. Few noteworthy exceptions in this context are: (i) the tricyclic norbornyl systems 141 studied by Hoffman;[69] (ii) 5-substituted-2-methyleneadamantanes 142 studied by le Noble;[24f] (iii) the recent reports by Halterman[25b] on 3,3-diarylcyclopentenes 31 and Ohwada[26] on spiro[cyclopent-2-ene-1,9'-fluorenes] 34 and very recent report of Vogel[70] on endo, endo-disubstituted-bicyclo[2.2.2]octene 143. While the work of Hoffman and



141

X=NSO_2Ph, O, CH_2, CMe_2.

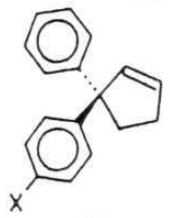
Reagents: CCl_2, 9-BBN, H_2/Pt, HN=NH.



142

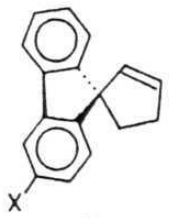
X=F

Reagents: m-CPBA, CCl_2, BH_3, $Hg(OAc)_2$, CF_3COOH.



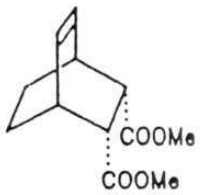
31

X=NO_2, Cl, Br, OMe, NMe_2.
Reagents: OsO_4.



34

X=NO_2, F, OMe.
Reagents: mCPBA.



143

Reagents: OsO_4, mCPBA, BH_3, PhSeCl, PhSCl.

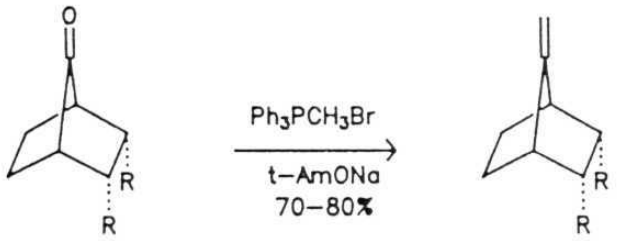
le Noble was known before we began our present studies, the other reports appeared during or after the completion of this work.

To further extend the scope of our initial observation of the profound effect of remote endo-substituents on the face selectivity at a distal stereogenic center, we have ventured to investigate the electrophilic additions to 7-methylene norbornane derivatives[71] which have the same advantageous feature of sterically equivalent π-faces in a conformationally rigid framework.

Synthesis of 2,3-endo,endo disubstituted-7-methylenenorbornanes:

2,3-endo,endo-7-Methylenenorbornanes 144a,b,e were readily synthesized from the corresponding 7-norbornanones 47a,b,e via Wittig alkenylation ($Ph_3P^+CH_3Br^-$, $t\text{-}C_5H_{11}O^-Na^+$, 70-80%), Scheme 23. In the case of the diester 47a, one of the ester groups epimerized to some extent (ca. 20-30%) under the basic conditions of Wittig reaction.

SCHEME 23



47a R=COOMe

47b R=CH_2OMe

47e R=Ethyl

144a,b,e

Stereochemistry of 7-methylenenorbornanes 144a,b,e:

The stereochemistry of the required endo,endo-compounds 144a,b,e was ensured on the basis of relatively greater shielding of $C_{5,6}$ resonances due to γ-steric effect of endo-substituents,[39] see Table 12. The two fold symmetry of 144a,b,e was further confirmed by their 7 line ^{13}C NMR spectra and the appearance of exocyclic methylene proton signals as singlets at δ 4.66, 4.56 and 4.58 in the ^{1}H NMR spectra of 144a, 144b, and 144e, respectively.

Table 12. ^{13}C NMR resonances of C_5-C_8 in 144a,b,e

Substrate	C_5,C_6	C_7	C_8
144a	23.29	155.65	98.77
144b	21.35	158.47	96.71
144e	20.76	160.36	95.47

Epoxidation:

Epoxidation of endo,endo-7-methylenenorbornane derivatives 144a,b,e with per-acid reagent, an electrophilic process, was investigated. The olefins 144a,b,e were treated with mCPBA in dichloromethane at 0-5°C to give a mixture of diastereomeric syn-145a,b,e and anti-146a,b,e epoxides, Scheme 24. The syn : anti ratios of epoxides formed are shown in Table 15 and were determined from the ^1H NMR integration of the crude reaction mixture. The mixture of epoxides 145a and 146a in the case of diester derivative were separated by column chromatography. The separation of other two pairs of epoxides derived from 144b, and 144e was not possible because of decomposition during separation. However, high resolution ^1H NMR data on crude mixtures enabled identification of each isomer.

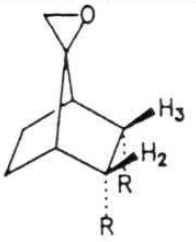
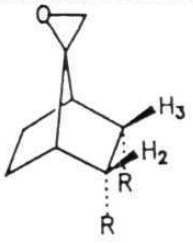
The results in Table 15 demonstrate that the electron withdrawing ester substituents in 144a direct the addition of per-acid reagent preferentially from syn-face (26 : 74). There is a complete reversal in the selectivity in 144e with electron donating ethyl substituents in which the reagent approaches predominantly from the anti face (70 : 30). The dimethoxy derivative 144b shows moderate anti-preference (55 : 45).

Streochemical assignments:

The stereochemical assignments were made on the basis of relatively greater deshielding of H_2,H_3 exo-protons in

the syn-epoxides 145a,b,e compared to anti-epoxides 146a,b,e, Table 13 (also see, Figs.40-42 in Section V).

Table 13. ^1H NMR resonances of $H_{2,3}$ in syn-145a,b,e and anti-146a,b,e.

Substrate	 syn-145a,b,e $H_{2,3}$	 anti-146a,b,e $H_{2,3}$
R = COOMe	3.42	3.24
R = CH_2OMe	2.73	2.52
R = Ethyl	2.26	2.04

Hydroboration:[72]

The olefins 144a,b,e on treatment with diborane followed by alkaline-H_2O_2 oxidation furnished a mixture of syn-147a,b,e and anti-148a,b,e primary alcohols, Scheme 24. The ratios of syn and anti products were obtained from the ^1H NMR integration of the crude reaction mixture and are shown in Table 15.

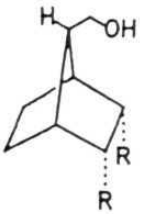
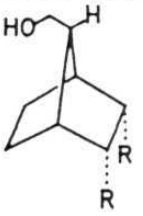
Again the pattern of selectivities remains the same, the electron withdrawing substituents directing preferential syn-attack and electron donating groups directing anti-attack. The observed selectivities in this case are not as

high as in the case of epoxidation.

Stereochemical assignments:

The stereochemical assignments again follow from the deshielding influence of OH group on H_2,H_3 exo-protons in syn-alcohols compared to anti-alcohols. ^{13}C NMR data can also be used as an additional probe in this case to further confirm the stereochemical assignments. The OH group of hydroxymethyl moiety at C_7 shields the resonances of carbon atoms underneath. Thus, C_5,C_6 resonances in anti-alcohols 148a,b,e are shielded by about 3 ppm compared to same resonances in syn-alcohols 147a,b,e, Table 14. Similarly, the relative shielding effect of OH group is also discernible in C_2,C_3 resonances in syn-series 147a,b,e (see, Figs.43-46).

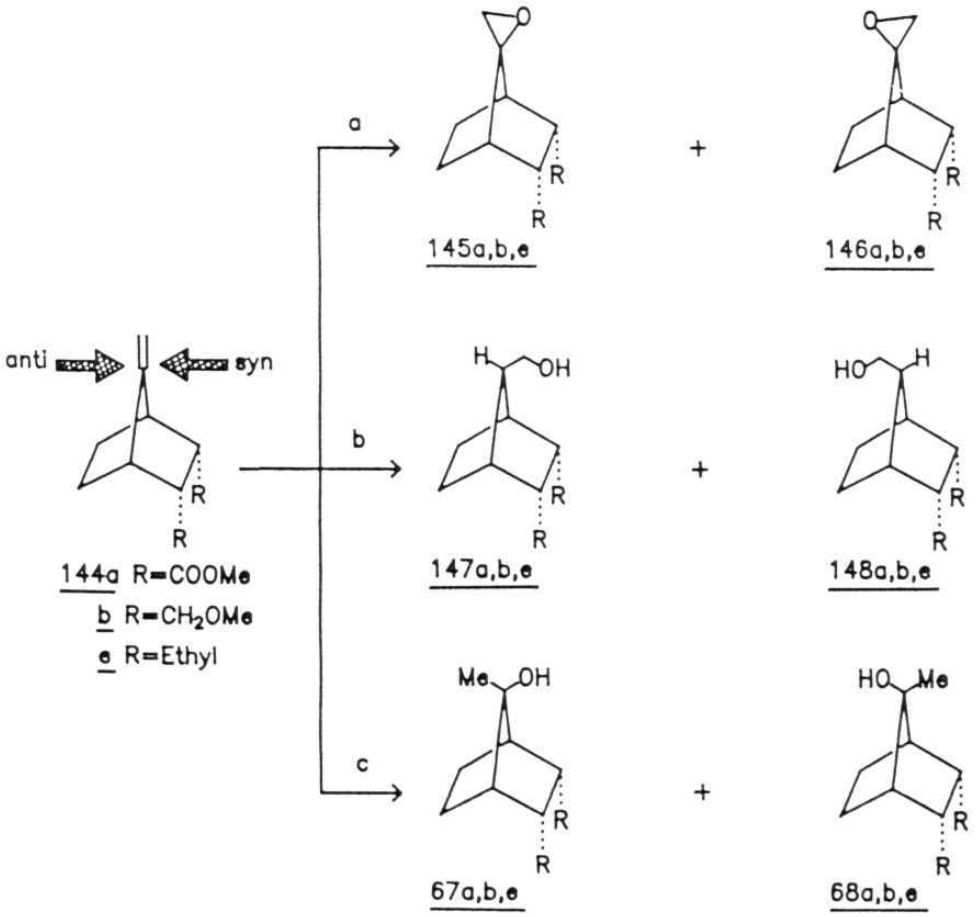
Table 14. ^{13}C NMR resonances of $C_{5,6}$ in syn-147a,b,e and anti-148a,b,e.

Substrate	 syn-alcohol	 anti-alcohol
	C_5,C_6	C_5,C_6
R = COOMe	24.64	21.64
R = CH_2OMe	22.88	19.94
R = Ethyl	22.17	19.17

Oxymercuration-demercuration:[73]

The treatment of olefins 144a,b,e with $Hg(OAc)_2$ followed by demercuration with $NaBH_4$ furnished a mixture of syn-67a,b,e and anti-68a,b,e tertiary alcohols, Scheme 24. The ratios of syn : anti products were obtained from the ^1H NMR integrations of the crude reaction mixture and are shown in Table 15. The diester compound 144a gave almost exclusively 67a as the only detectable isomer (^1H & ^{13}C NMR) and did not require further purification. The diastereomeric

SCHEME 24



Reagents: a) m-CPBA, CH_2Cl_2, 0-5°C; b) B_2H_6-THF, H_2O_2-aq.NaOH; c) $Hg(OAc)_2$, aq.THF, $NaBH_4$-NaOH.

mixture of alcohols derived from 144b were separated by column chromatography. In the case of 144e only the major product was obtained after purification. The mixture of products obtained here are the same as those obtained in the case of methyllithium additions to corresponding 7-norbornanones (vide supra, Scheme 5) except that these two reactions lead to the opposite isomers as major/exclusive products, e.g., the major product formed in the former reaction is minor/traces in the latter reaction and vice-versa.

Table 15. Product ratios in electrophilic additions to 144a,b,e

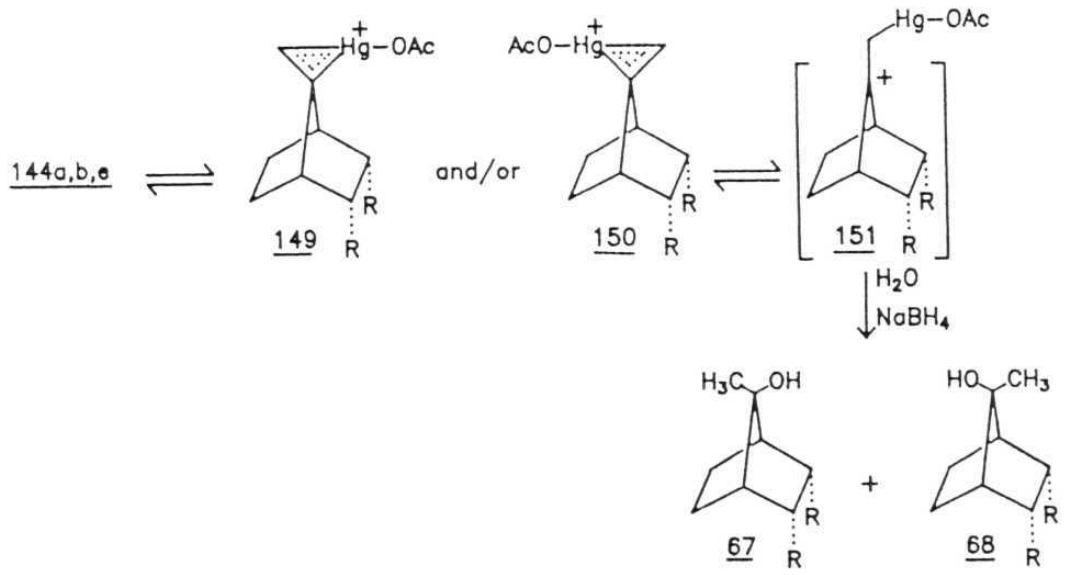
Substrate	syn : anti ratios (%)		
	epoxidation	hydroboration	oxymercuration
144a	74 : 26	41 : 59	>95 : trace
	145a 146a	147a 148a	67a 68a
144b	45 : 55	56 : 44	40 : 60
	145b 146b	147b 148b	67b 68b
144e	30 : 70	62 : 38	17 : 83
	145e 146e	147e 148e	67e 68e

Interpretation of results:

The oxymercuration step involves a sequence in which an electrophilic attack by $Hg(OAc)_2$ is followed by nucleophilic (e.g., H_2O) attack. The demercuration step reductively

breaks the C-Hg bonds. The initially formed mixture of syn- and anti-mercurinium ions (149 and 150), in a reversible process undergo nucleophilic capture in a rate limiting step via the intermediacy of the open chain cation 151, as shown in Scheme 25. Thus, the observed selectivity is actually the outcome of nucleophilic addition to carbocation intermediate 151. There is no direct experimental evidence to show the preferential approach of the electrophile, $Hg(OAc)_2$ to to the reaction center. Since both syn and anti complexes 149 and 150 pass through the common intermediate 151, the observed selectivities of the final products does not give

SCHEME 25



any indication about the predominant approach of the electrophile. However, an intuitive guess, based on earlier precedents with other electrophiles is that syn-complex 149 could be formed predominantly in the case of 144a with electron withdrawing groups and anti-complex 150 in the case of 144e with donor groups.

Broughton et.al.,[74] in their very recently reported work have contradicted the above mechanism based on theoretical calculations on 7-methylene norbornane derivatives. Calculated PM3 molecular electrostatic potentials show anti-face to be more attractive to an electrophile when the substituents are electron withdrawing such as R=COOMe (144a) or F. For electrophiles such as $Hg(OAc)_2$ and I^+, having large charges (I^+, 0.83; Hg^+, 0.75), it was suggested that electrostatic asymmetry controls the selectivity and hence anti-attack is favored. Subsequent back-side attack by nucleophile (e.g., H_2O) would open the anti-mercurinium ion 150 (R=COOMe) to furnish syn-alcohol 67a, as observed by us experimentally.

Overall, the results of electrophilic additions to 144a,b,e displayed in Table 15 show a crossover in syn/anti approach of the electrophiles in going from 144a to 144e. The π-face stereoselection observed here is moderate in the case of additions proceeding through cyclic transition states (e.g. epoxidation and hydroboration) but is significantly enhanced in the case of the more polar addition (oxymercuration). The electrophiles attack 144a and 144e predominantly from syn- and anti-face, respectively. The dimethoxy compound 144b shows a modest preference for the anti-approach. These results appear in general to be consistent with the Cieplak hyperconjugative model in which the stabilizing interaction between the electron rich anti-

periplanar σ bond and the developing σ^* orbital lowers the transition state energy. Accordingly, irrespective of which reacting partner contributes the bonding electrons, σ^* orbitals would attract electron density through the same directional preference, i.e., more electron rich σ bond. In agreement with this prediction, electrophiles exhibit the same face selectivity in approach to 144a,b,e, as do nucleophiles in their approach to 47a,b,e.

II.8 2-endo-SUBSTITUTED-7-ISOPROPYLIDENENORBORNANES:

Although some of the electrophiles such as per-acid, BH_3 and $Hg(OAc)_2$ reacted with 7-methylenenorbornane derivatives,[71] the reactivity of the exocyclic double bond is poor towards most other common electrophiles. Another serious problem is the mechanistic ambiguity in these systems. There are basically two ways in which electrophilic addition to an olefin can take place. The first is a one step process in which both the carbon atoms of the olefin are attacked simultaneously, e.g. epoxidation and hydroboration, both of which proceed via cyclic transition state involving one-step mechanism. In the second, a two step process is involved, with initial attack by an electrophile followed by combination of the resulting cation intermediate with a negatively charged nucleophile. The intermediate cation in the two-step process may be open chain or cyclic depending on several factors. In the case of open chain intermediate, the stability of cation determines which of the two carbon centers be attacked by E^+. Therefore, addition of those

electrophiles to 7-methylenenorbornanes which proceed through two-step mechanism, e.g. $Hg(OAc)_2$, are ambiguous in the sense that the original direction of the electrophilic attack is not revealed directly. Whereas, in the case of epoxidation and hydroboration reactions, the original entity added from the electrophilic reagent remains in the product without any change in its position and hence its location reveals the direction of reagent approach.

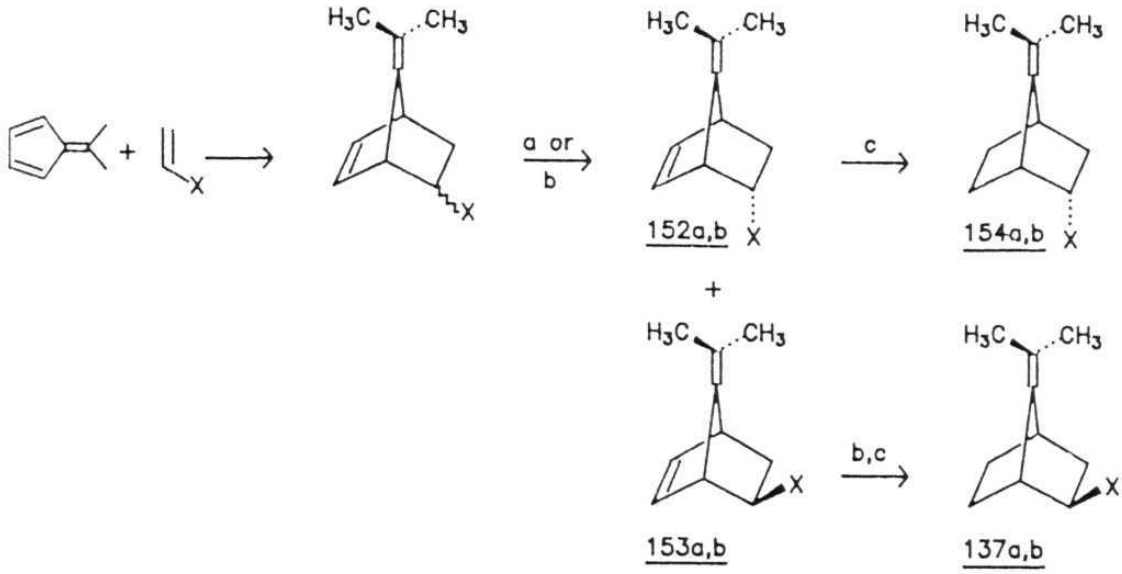
In view of the controversy regarding the preferred direction of approach of charged electrophiles[74] such as $Hg(OAc)_2$ or halonium ions in 7-methylenenorbornane derivatives, we designed additional new experiments to sort out the issue. 7-Isopropylidene norbornyl systems attracted our attention as the use of the isopropylidene unit instead of methylene offers significant advantages. From an experimental point of view the double bond becomes more reactive, enabling the addition of electrophiles which were unsuccessful earlier. Further, unlike in 7-methylenenorbornanes, the site of electrophilic attack is likely to be at C_7 and not at C_8, a factor which is crucial for interpretation. Finally, the mechanistic details of electrophilic attack are unambiguous and the steric neutrality on the two π-faces is maintained.

Synthesis of 7-isopropylidenenorbornanes:

7-Isopropylidenenorbornanes 154a,b were readily prepared *via* the known Diels-Alder reaction[75] between 6,6-

dimethylfulvene and acrylonitrile or methyl acrylate, Scheme 26. A mixture of endo and exo-isomers were obtained in each case. The required endo-products were separated from the reaction mixture through slow fractional crystallization. The regioselective reduction of the endocyclic norbornene double bond in 152a,b and 153a,b using diimide furnished 7-isopropylidenenorbornanes 154a,b and 137a,b, Scheme 26.

SCHEME 26



Reagents: (a) fractional crystallization; (b) column purification; (c) diimide reduction.

Bromination:

Aqueous N-bromosuccinimide is a convenient source of bromonium ion, Br^+. The treatment of 154a,b with NBS in 9:1 DME-H_2O at 0-5°C directly furnished a mixture of allylic bromides 155a,b and 156a,b, Scheme 27. All the work-up operations were carried out below 10°C and the ^1H and ^{13}C

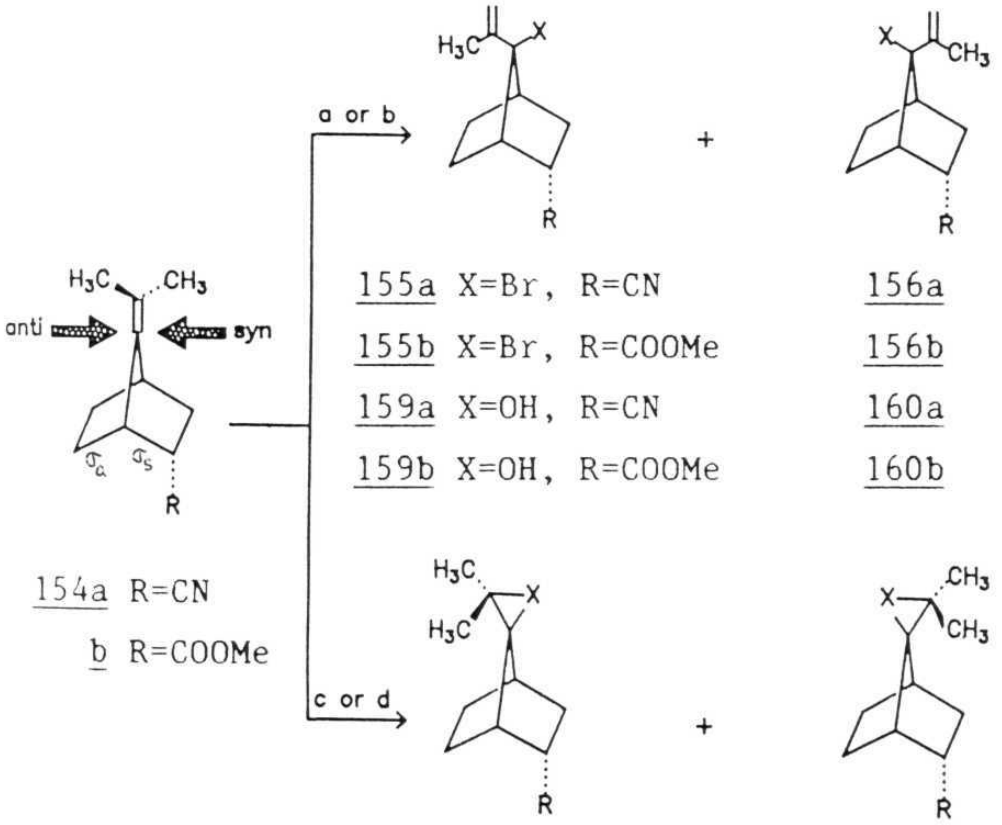
NMR spectra were recorded immediately as the mixture of products showed high tendency for allylic rearrangement at room temperature. Small amounts of pure diastereomers in each case were obtained by quickly eluting the mixture on a preparative tlc plate. The stereochemical assignments were based on chemical shift value of H_2 exo-protons in the ^1H NMR which appeared at δ 3.52, 3.60-3.46 for syn-155a,b and δ 2.74, 2.77 for anti-156a,b, respectively. The ratios as determined by the ^1H NMR spectra of crude reaction mixture are summarized in Table 16. The results demonstrate that the electron withdrawing CN and COOMe groups again induce syn-preference. There is also no ambiguity about the initial direction of attack of Br^+. Since the nucleophilic attack on the bromonium ion is followed by an elimination to give the olefins 155a,b and 156a,b, the location of the bromine atom in these products directly reveals the direction of the initial electrophilic attack. Based on the observed product ratios, the charged electrophile Br^+ prefers to approach the syn-face of 154a and 154b.

Dichlorocarbene Additions:

Dichlorocarbene is a neutral electron deficient species, which can be generated in situ by thermal decomposition of sodium trichloroacetate. Reaction of 154a,b with in situ generated CCl_2 produced a mixture of syn- and anti-adducts 157a,b and 158a,b, Scheme 27. The product ratios were obtained from the ^1H NMR spectra of the crude reaction mixture and are shown in Table 16. The chlorine atoms in

the syn-adduct manifest a similar relative deshielding effect on H_2-exo protons as generally observed. The diastereomeric mixtures in both the cases were separated by column chromatography.

SCHEME 27



Reagents: a) NBS, DME-H_2O (9:1), 0-5°C; b) $^1O_2$, hv, methylene blue, CH_2Cl_2; $NaBH_4$, MeOH; c) $Cl_3CCOO^-Na^+$, DME-TCE, reflux; d) mCPBA, Na_2CO_3, CH_2Cl_2, 0-5°C.

Singlet Oxygenation:

Reaction of olefins 154a,b with oxygen that has been photosensitized using a dye (methylene blue) furnished a mixture of syn-and anti-allylic hydroperoxides. The mixture of hydroperoxides were not examined but directly reduced with $NaBH_4$ to allylic alcohols syn-159a,b and anti-160a,b for characterization, Scheme 27. The product ratios were obtained from ^1H NMR integration of crude mixture of allylic alcohols, Table 16. Stereochemical assignments were based on the lower field position of H_2 exo-proton in syn-alcohols compared to anti-alcohols. The H_2 exo-protons appeared at δ 3.42-3.30, 3.42-3.32 for syn-159a,b and 2.91-2.78, 2.90-2.78 for anti-160a,b alcohols, respectively (see, Figs.47,48 in Section V).

Epoxidation:

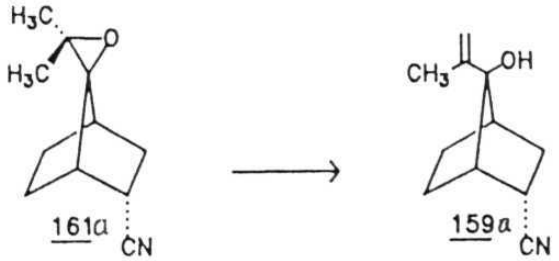
Epoxidation of 154a and 154b with mCPBA in methylene chloride at 0-5°C furnished a mixture of syn-161a,b and anti 162a,b epoxides, Scheme 27. The syn : anti ratios were determined by the ^1H NMR integrations of crude reaction mixtures and are shown in Table 16. The major isomers in both the cases were isolated by means of column chromatography. The stereochemical assignments were based on greater deshielding of H_2 exo-protons in syn-epoxides compared to anti-epoxides which appeared at δ 3.20-3.08, 3.27-3.15 for syn-161a,b and 2.91-2.78, 2.98-2.82 for anti-162a,b in the ^1H NMR spectra. The syn-epoxide 161a on keeping for longer periods in $CDCl_3$ solution in the NMR tube

Table 16. **Ratios of syn and anti-addition products[a] observed in reactions of 154a,b.**

	Br^+		$:CCl_2$		$^1O_2$		m-CPBA	
Compound	syn	anti	syn	anti	syn	anti	syn	anti
154a	72	28	78	22	78	22	77	23
	155a[b]	156a[b]	157a	158a	159a	160a	161a	162a
154b	59	41	60	40	61	39	62	38
	155b[b]	156b[b]	157b	158b	159b	160b	161b	162b

a) Product ratios (±5%) are based on the ^1H NMR integration of the reaction mixture; (b) Exhibits marked propensity for allylic rearrangement.

underwent epoxide opening accompanied by α-proton elimination, probably catalyzed by trace amounts of acidic impurities in the solvent, to furnish the allylic alcohol 159a. This alcohol was found to be identical with the major product obtained from the photooxygenation reaction of 154a (vide supra). This confirmed the internal consistency in stereochemical assignments and also provides strong



supporting evidence for the fact that the major products in both the reactions (i.e. photooxygenation and epoxidation) resulted as a consequence of preferential syn-attack by the reagent.

Interpretation of results:

The above results[76] (Table 16) confirm that even a single electron withdrawing substituent in the endo-position is capable of inducing facial discrimination and leads to products derived from electrophilic addition, preferentially to the syn-face, thus reinforcing our earlier observations. There is also no ambiguity about the initial direction of attack of reagent in these systems. Particularly in the reactions of NBS and $^1O_2$, the entities added from the reagent to the reaction center remain at the position of initial attack and act as convenient labels to establish the preferred direction of reagent approach.

To delineate the nature of the electronic control of the observed selectivities, we carried out[#] a topographical analysis of the MESPs of 154a,b at the ab initio level with the 6-31G basis set using the parallel SCF program INDMOL.[77] Attention was focused particularly on the MESP minima whose depth generally signifies a greater concentration of

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[#] Theoretical studies involving ab initio electrostatic potentials were carried out by Prof. S.R. Gadre and R.N.Shirsat, University of Poona, Pune, India.

electron density. For both 154a,b, the MESPs about the two π-faces are unsymmetrical, with the (3,+3) critical point (CP) on the anti-face consistently having a more negative value (Table 17). However, as the MESP value at the CPs are significantly less negative than those obtained for typical C=C bonds (the MESP minimum for ethylene is -0.0383 a.u.), electrostatic influences are probably not of primary importance in determining the face selectivities in the present system.

In order to confirm the potential role of orbital interactions in determining the face selectivities in these substrates, the unsymmetrical donor abilities of the σ_s and σ_a bonds were characterized in terms of the electron densities at the corresponding bond CPs (Table 17). In the

Table 17. MESP[a] at (3,+3) minimum and electron density at bond CP (all values in a.u.)

Compound[b]	MESP at CP		Density at bond CP	
	syn	anti	σ_s	σ_a
154a	-0.0174	-0.0222	0.2114	0.2172
154b	-0.0278	-0.0305	0.2109	0.2171

(a) A CP of a scalar field f is one where $\nabla f=0$. The CPs are classified in terms of the eigenvalues of the Hessian. The MESP and bond CPs are (3,+3) and (3,-1) types in the respective scalar fields.

systems 154a,b, with electron withdrawing groups, the σ_a bond consistently has a greater density. Operation of Cieplak type[13] orbital interactions would then lead to the observed syn-face selectivity.

Semiempirical MO calculations[#] on the bromonium ion intermediates resulting from 154a,b as well as carbene addition transition states lead to several additional insights (Table 18). Optimization of the classical bromonium ion intermediates at the PM3 level confirm that Br^+ prefers to attack the C-7 center, relative to C-8 (by 6-7 Kcal/mol), as a less strained tertiary carbocation is formed in the former. The computed syn-anti energy differences are small. Nevertheless, for both 154a and 154b, the ion formed by addition to the syn-face is consistently more stable, in agreement with the observed face selectivities. Interestingly, the preference is larger for the ions formed by C-7 attack compared to C-8, particularly for 154a [$\triangle$E (anti-syn)=0.8 and 0.3 Kcal/mol, respectively). One expects greater unfavorable electrostatic interactions between the Br^+ ion at C-7 and syn-face of 154a. These are evidently overcome by effective orbital stabilization involving the Br-C_7 σ^* MO and the relatively electron rich anti-periplanar σ_a bond.

[#] Semi-empirical MO calculations and transition state energetics were carried out by Prof.J.Chandrasekhar and B.Ganguly, IISc., Bangalore, India.

Transition state energies determined for CCl_2 addition to 154a,b using the AM1 procedure[78] are also consistent with the observed stereoselectivities. Since the least-motion pathway for the addition of a carbene to an olefin is a forbidden pathway, the transition structure is highly unsymmetrical. The carbene forms a bond effectively to one of the olefinic carbon atoms with a CCC angle of ~90°. The chlorine atoms are tilted towards the other carbon, which has a planar coordination characteristic of a carbocation. These features have significant consequences for the face selectivities of 154a,b. In view of the unsymmetrical nature of the olifines, two sets of first order saddle points, characterized by a closer approach of the carbene to

Table 18. **Calculated heats of formation in kcal mol^{-1} (1 cal=4.184 J) of classical intermediates formed by bromonium ion additions and transition states for dichlorocarbene additions to 154a,b.**

Compound	Site of electrophilic approach	Br^{+a} syn	Br^{+a} anti	$:CCl_2{}^{b}$ syn	$:CCl_2{}^{b}$ anti
154a	C-7	228.64	229.41	91.53	92.37
	C-8	236.29	236.55	93.17	93.21
154b	C-7	109.05	109.26	-23.11	-22.52
	C-8	115.64	115.76	-21.66	-21.65

(a) PM3; (b) AM1.

C-7 or C-8, are obtained for the syn as well as anti-face additions. Interestingly, the energetically favored transition states correspond to CCl2 attack at C-7. As a result, the newly formed C-C bond is more responsive to the unsymmetrical orbital effects from σ_a and σ_s orbitals. Further, the chlorine atoms are tilted upwards in the corresponding transition states, precluding any contribution from electrostatic interactions from the norbornyl unit. Overall, a clear preference for syn-face attack results. Interestingly, for the transition states for attack at C-8, there is negligible face selectivity. Orbital effects and electrostatic interactions seem to effectively cancel each other.

II.9 5-endo-SUBSTITUTED-7-ISOPROPYLIDENENORBORNENES:

The interesting results with substituted 7-isopropylidenenorbornanes 154a,b[76] have provided an impetus to extend these studies to the 7-isopropylidenenorbornene systems,[79] which are of intrinsic interest due to the presence of much acclaimed homoconjugative interaction between the two olefinic bonds.[80] Several subtle electronic effects have also been proposed by Paquette and Gleiter[81] to account for the dependence of the face selectivities on the nature of electrophile in additions to unsubstituted 7-isopropylidenenorobornene.[82] Therefore, studies on endo-substituted 152a,b (Scheme 28) with a variety of electrophiles were expected to unravel the direct response of the substituent on the face-selectivity without perturbing the steric environment.

CCl_2 addition,[#] singlet oxygenation, and epoxidation of 7-isopropylidenenorbornenes:

7-Isopropylidenenorbornenes 152a,b were subjected to CCl_2 addition, epoxidation and singlet oxygenation under the same conditions as described earlier for 154a,b (Scheme 27). The CCl_2 addition to 152a,b furnished syn-163a,b and anti-164a,b adducts in 70% yield, Scheme 28. The diastereomeric pairs in both the cases were separated by column chromatography. The product ratios of syn and anti-adducts 163a,b and 164a,b were determined from the ^1H NMR and also from the isolated yields of pure isomers, Table 19. The mixture of allylic peroxides obtained initially by the photooxygenation of 152a,b were directly reduced with $NaBH_4$ to allylic alcohols 165a,b and 166a,b in 80-90% yield for the purpose of characterization. The minor isomer 166a (4%) was not isolated but its presence was inferred from high resolution ^1H NMR spectrum. The ratios of diastereomeric pairs of allylic alcohols were obtained both by the ^1H NMR and GLC, Table 19. Per-acid epoxidation of 152a,b furnished a mixture of syn-167a,b and anti-168a,b in high yield (>90%). The ^1H NMR of the crude product from 152a did not indicate any peaks corresponding to the isomer 168a. This was further confirmed by hydrogenating the crude reaction mixture and comparing the ^1H NMR spectrum with previously

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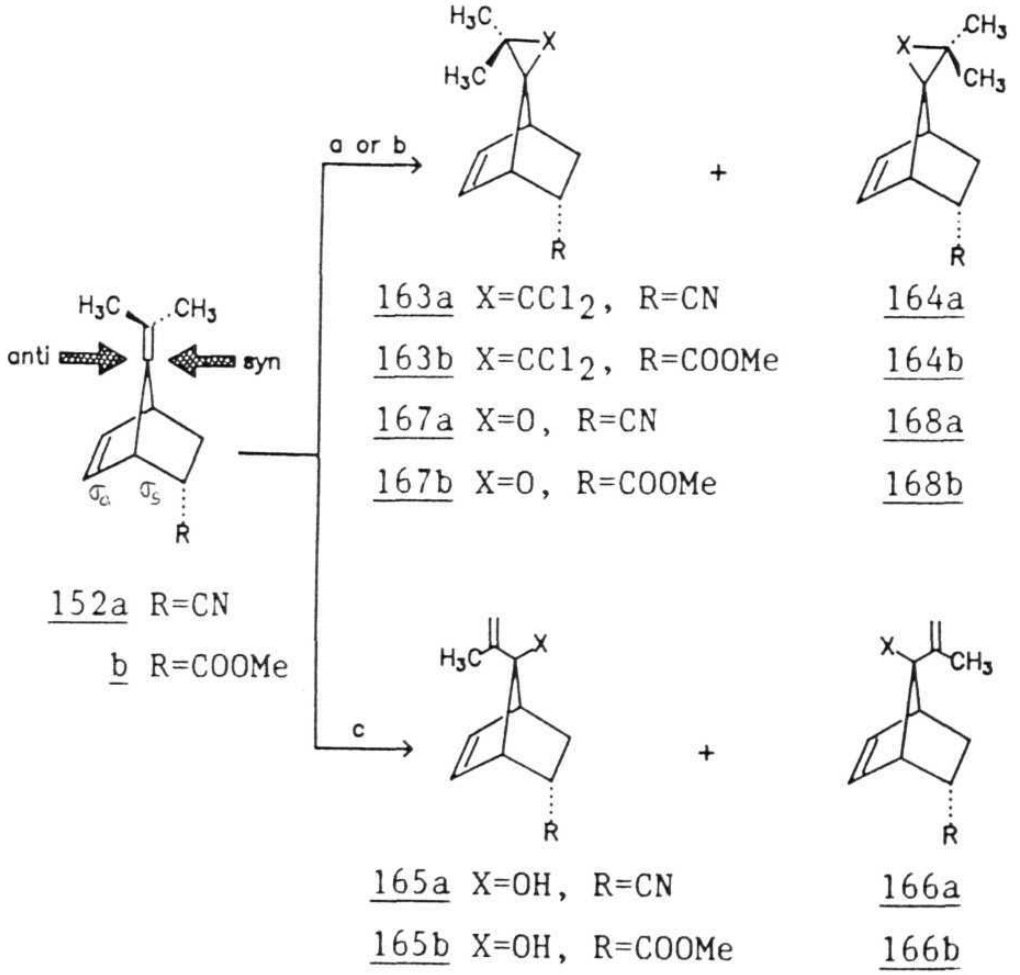
[#] Dichlorocarbene additions to 154a,b and 152a,b were carried out by Mr. G. Gunasekharan. I thank him for his help.

obtained saturated epoxides 161a and 162a. The ^1H NMR spectrum of the crude mixture after hydrogenation matched well with the major isomer obtained in the epoxidation of 154a. This confirmed the predominant syn-approach of the reagent in both 152a and 154a. Epoxidation of ester derivative 152b also furnished a mixture with syn epoxide 167b as the major product (>85%, determined by ^1H NMR) which on

SCHEME 28



152a R=CN
b R=COOMe

163a X=CCl_2, R=CN — 164a
163b X=CCl_2, R=COOMe — 164b
167a X=O, R=CN — 168a
167b X=O, R=COOMe — 168b

165a X=OH, R=CN — 166a
165b X=OH, R=COOMe — 166b

Reagents: a) $CCl_3COO^-Na^+$, DME-TCE, reflux; b) m-CPBA, Na_2CO_3, CH_2Cl_2, 0-5°C; c) $^1O_2$, hv, methylene blue, CH_2Cl_2; $NaBH_4$, MeOH.

column purification and hydrogenation gave the previously characterized saturated syn-epoxide 161b.

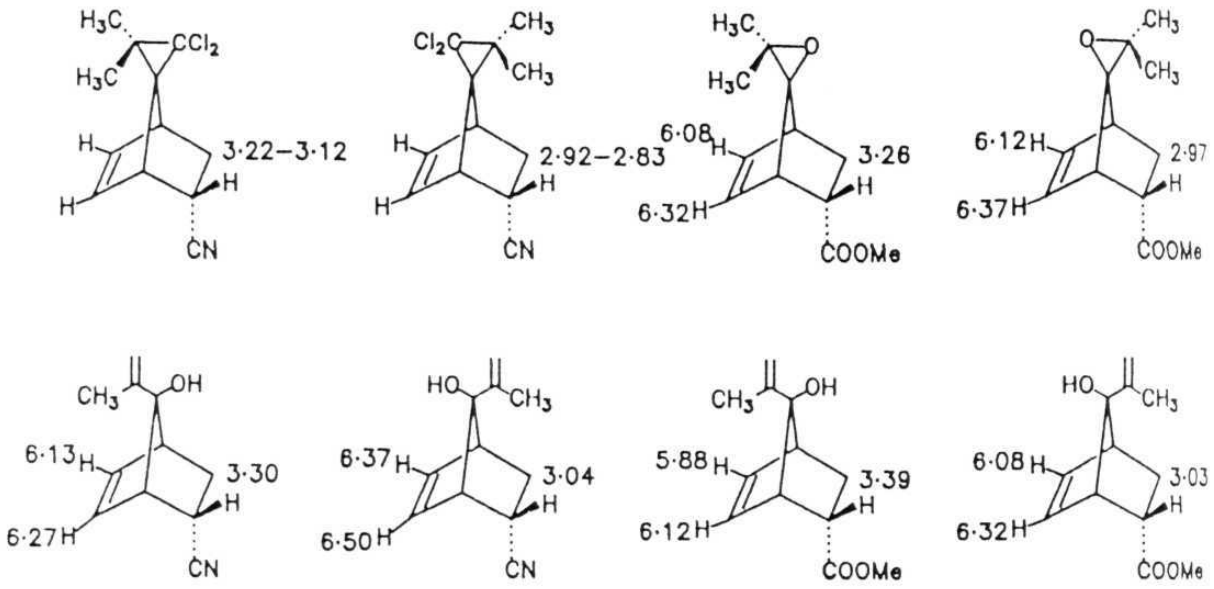
Table 19. **Ratios of syn- and anti-addition products observed in reactions of 152a,b**

	CCl_2		$^1O_2$		mCPBA	
Compound	syn	anti	syn	anti	syn	anti
152 (R=H)[81]	12	88	86	14	66	34
152a	35	65	96	4	>90	traces
	163a	164a	165a	166a	167a	168a
152b	34	66	92	8	>85	<15
	163b	164b	165b	166b	167b	168b

Stereochemical assignments:

The stereochemical assignments to all the adducts obtained were based on relative greater deshieling of H_5-exo protons in syn-series and H_2, H_3 olefinic protons in the anti-series when compare with the chemical shift of these protons in their respective counterparts. The chemical shift values of H_2, H_3 and H_5 for the four diastereomeric pairs are shown on the structures (Scheme 29, also see Figs.49-52 in Section V). In few cases the assignments were cross-checked by hydrogenating the pure isomer to corresponding saturated derivatives.

Scheme 29



Interpretation of results:

The fact that certain electrophiles add predominantly from the side of the cyclopentene C=C bond which is intrinsically favorable for steric reasons and certain other prefer to approach from the sterically more demanding ethano-bridge side in the parent 7-isopropylidenenorbornene system 152 (R=H) is rather intriguing. Paquette and Gleiter[81] rationalized this behavior in terms of cyclic and open cation intermediates and recognized that the weak electrophiles require bridged ions 169 whereas powerful electrophilic reagents react via open ions 170. The corresponding transition states for weak electrophiles are

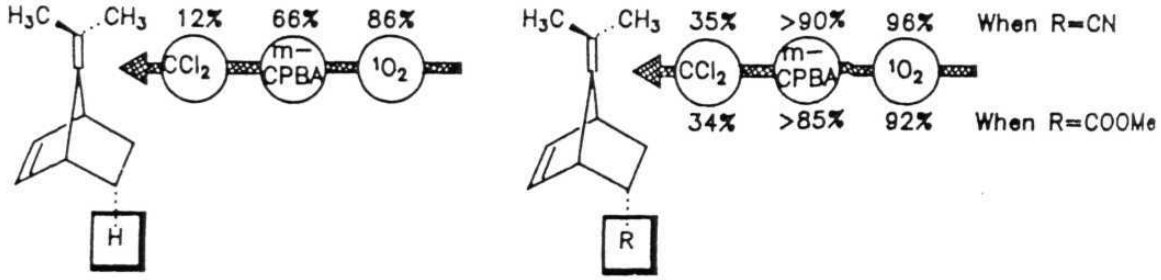
169 170

stabilized by the homoconjugative interactions of the endocyclic double bond and hence contra-steric attack (approach from ethano bridge) is favored. The strong electrophiles which are not dependent on the development of long-range stabilization were believed to be influenced by the prior coordination with the endocyclic double bond, therefore, preferential approach from the double bond side is observed.

Houk and coworkers[83] in their recently reported work attributed the observed inconsistency in electrophilic additions to 7-isopropylidene norbornenes to "reagent specific electrostatic effects". The 6-31G* electrostatic potentials of 7-methylenenorbornene showed greater electron density on the face containing etheno-bridge and attack from this side should be preferred by the positively charged or strong electrophiles. The weak electrophiles which prefer contra-steric approach (from ethano bridge) bear lone-pair electrons and have high electron densities on their surfaces. They are effectively "negative" or "nucleophilic" in their ground state and hence avoid more negative π-face of the bridge olefin (C_7-C_8). Further, simple computations at 6-31G* level on the relative energies of 7-methylenenorbornene with or without an added partial charge (both positive and negative charges were considered) indicated that the cyclopentene C=C double bond stabilizes a positively charged electrophile and destabilizes a negatively charged electrophile.

Irrespective of the guiding force dictating the preferred approach of an electrophile, the results in Table 19 demonstrate that endo-electron withdrawing substituents consistently induce syn-preference and tilt the balance more towards the product derived from syn-attack compared to the parent system for any given electrophile. The intrinsic steric bias existing in system 152 is not altered at all by the placement of substituent(s) in endo-disposition at C_5 or C_5,C_6 and hence the product distribution in the parent system for any given electrophile may be taken as base line to evaluate the π-facial selectivity induced by endo-substituent(s). The results of electrophilic additions to parent system 152 (R=H) and endo-derivatives 152a and 152b, shown in Table 19, are illustrated in Scheme 30 on the structures to highlight the syn-preference induced by CN and COOMe groups.

Scheme 30



In order to interpret the observed substituent effects, a topographical investigation of the electron density distribution $\rho(r)$ and molecular electrostatic potentials (MESP) for 152a and 152b was carried out at the ab initio level using the parallel SCF program INDMOL,[77] as earlier. For a bond between a pair of atoms in a molecule, there

exists a (3,-1) saddle point (termed as bond Critical point, CP)[84] in $\rho(r)$. The density at these bond CPs gives an indication of donor strengths for hyperconjugative interactions and can be used to explain the stereoselection. The densities at bond CPs for systems 152a,b with the 6-31G basis set are reported in Table 20. This data reveals that an electron withdrawing substituent at C_5 increases the density at the C_3-C_4 (σ_a) bond CP, relative to that at the C_4-C_5 (σ_s) bond CP (see structures 152a,b in Scheme 28). The enhanced asymmetry should favor electrophilic attack from the syn-face on the basis of the Cieplak hyperconjugative model.[13]

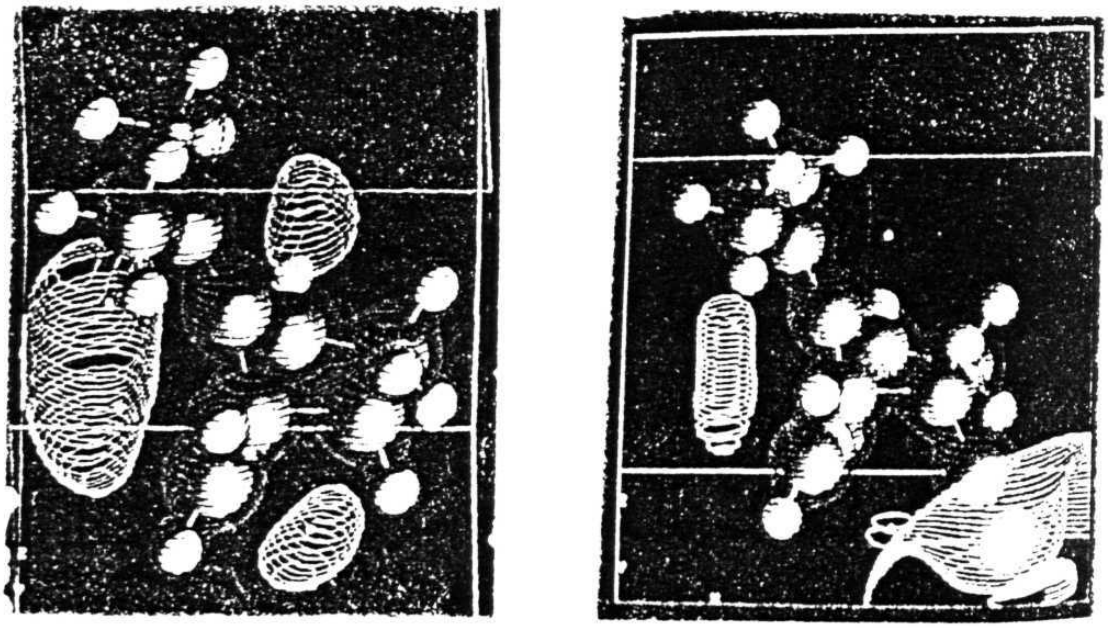
Table 20. Electron density at bond CPs and MESP minima (all values in a.u.) from ab initio calculations using MNDO optimized geometries.

	σ_s	σ_a	MESP at CP			
			C_7=C_8		C_2=C_3	
			syn	anti	exo	endo
152a	0.2139	0.2285	-0.0380	-0.0463	-0.0464	-0.0339
152b	0.2982	0.2288	-0.0172	-0.0305	-0.0312	-0.0243

The computed MESPs provide valuable insights concerning the role of electrostatics in determining the face selectivities. For a typical olefin, there exist two (3,+3) minima

in the scalar field of V(r) on either side of the double bond [V(r)=-0.0383 a.u. for ethylene with the 6-31G basis)]. A negative minimum in V(r) is a signature of localization of electron density. For the unsubstituted system 152 (R=H), four such minima are obtained, as expected (Table 20). For the C_7=C_8 bond, the minimum towards the C_2=C_3-face is deeper. Interestingly, the isopotential surfaces for 152, R=H (Fig.X A, MESP=0.5, -0.02 and -0.09 a.u.) reveal that the negative contours of the two bonds merge, providing a visual definition of homoconjugation. Thus, the two double bonds reinforce electron localization and may direct electrophilic attack from the olefin face.

Fig.X



A B

The introduction of an endo-substituent produces a dramatic change in the MESPs. The values of V(r) at the minima around the exocyclic double bond are substantially

reduced. The isopotential surfaces for 152a (Fig.X B) show the extent to which the endo-cyano group drains the negative potential contours from the reaction sites. While the minima on the syn- and anti- faces are unsymmetrical, it is unlikely that electrostatics are important in these substituted derivatives in determining face selectivities. It may be expected that the MESP minima should be deeper than a certain threshold for electrostatic effects to play any discriminating role. A value of -0.0383 a.u., as found in ethylene may be taken as a practical guideline for electrostatic take-over.

Transition state energies calculated at the AM1 level[77] for CCl_2 addition to 152a,b though not in quantitative agreement with the experimental results, confirm the electronic role of endo-substituents in influencing face-selectivities (Table 21). Transition structures for carbene addition to olefins are generally unsymmetrical, with one C-C bond being formed to a greater extent and the chlorine atoms tilted towards the other olefinic carbon. For the present substrates, two sets of first order saddle points, characterized by a closer approach of the carbene to C_7 or C_8, are obtained for the syn- as well as anti-face additions. In 152a,b, carbene attack at both C_7 and C_8 are energetically feasible. Since the facial preferences derived from the resulting transition states are in opposing directions there is some ambiguity in the predicted

Table 21. Calculated Heats of Formation in Kcal mol^{-1} for the Transition States of CCl_2 addition to 152a,b.

Compound	Site of carbene attack	syn	anti	$\triangle E$
152 (R=H)	C-7	99.22	99.50	0.28
	C-8	100.42	99.97	-0.45
152a	C-7	132.12	133.20	1.08
	C-8	133.97	133.55	-0.42
152b	C-7	17.87	18.71	0.84
	C-8	19.55	19.09	-0.46

face-selectivity. However, the effect of endo-substitution is clear. For C_7 attack, even a single electron withdrawing group in 152a,b enhances the syn-preference, while the transition states for C_8 attack retain their energy difference favoring the anti-approach. The overall consequence is that the electron withdrawing groups reduce the preference for anti-face addition.

The above results demonstrate that orbital interactions involving endo-electron withdrawing groups consistently reduce the preference for the electrostatically favored anti-face selectivity in 7-alkenylnorbornenes.

III. SUMMARY

New probes for the study of electronic control of π-facial selectivities based on norbornyl systems have been designed which provide sterically neutral environment in a conformationally rigid framework with the provision of remote electronic fine-tuning using endo-substituents as convenient handles. New procedures of syntheses have been developed for these systems using known Diels-Alder protocol to provide the basic bicyclic framework followed by routine but unambiguous chemical transformations to obtain a series of endo-mono- and endo, endo-disubstituted-7-norbornanones, 7-norbornenones, bicyclo[2.2.2]octanones, 7-alkenylnorbornanes and a few related polycyclic norbornyl systems.

Employing endo, endo-disubstituted-7-norbornanones, we have successfully demonstrated the profound influence of endo-substituents in controlling π-facial selectivities during nucleophilic additions, the most dramatic being the reversal in going from 47a (16 : 84) bearing endo-ester groups to 47e (80 : 20) having endo-ethyl groups. Norbornenone systems with intrinsic steric bias have been used as probes to evaluate ground state geometric distortions vs electronic effects. The X-ray crystal structure of endo, endo-7-norbornenone diester 91a and theoretical calculations showed a tilt of the keto bridge away from the C=C bond making the double bond face sterically more open for the reagent approach. The observed face selectivities, however, show that electronic influence of the endo-substituent supersede the ground state geometric distortions. Monosubs-

tituted norbornyl systems provide the magnitude of selectivity induced by a single substituent and thus can be used successfully to extrapolate the selectivity in disubstituted norbornyl systems by simply calculating the algebraic sum of selectivities due to each individual substituent. Bicyclo[2.2.2]octanones not only offer a further testing ground for electronic control of selectivities but also the two possible endo-monosubstituted regioisomeric ketones serve as excellent probes to segregate electrostatic and orbital components. The observed selectivities in these systems are slightly diminished but generally consistent with those observed for norbornyl systems. The most striking feature common to all the substrates studied is that the electron withdrawing endo-substituents direct the nucleophilic addition from the syn-face whereas electron donating substituents induce anti-preference.

The majority of the results on nucleophlic additions to 7-norbornyl and related systems can be reconciled in terms of Cieplak's hyperconjugative model. Electrostatic effects too manifest themselves in certain cases but they can be overcome by the more prevalent orbital contribution, e.g. as in the case of 119b.

Electrophilic additions to 7-alkenylnorbornane derivatives constitutes an important body of results in view of the limited literature reports of such additions to sterically neutral systems. Hydroboration, epoxidation and oxy-

mercuration reactions on endo-substituted 7-methylene norbornane derivatives 144a,b,e reveal that the electron withdrawing groups direct the reagents from the syn-face while electron donating groups show anti-preference. Thus, a reversal in the product distribution is observed in going from 144a to 144e in all the cases studied. The reactions which proceed through cyclic transition state are less stereoselective (e.g. hydroboration and epoxidation) than those proceeding via ionic or polar intermediates (e.g. oxymercuration) The remote endo-substituents exert similar control on the "electrophilic reagent traffic" at a sterically neutral site as in the case of nucleophilic additions to endo-substituted-7-norbornanones and related systems. These results convincingly demonstrate that irrespective of which reacting partner contributes the bonding pair of electrons, the directional preference of the reagent approach remains the same. Only those models which predict the same direction for reagent approach in both nucleophilic and electrophilic additions may be considered to rationalize the observed selectivities. Among these, Cieplak's hyperconjugative model explains the observed experimental data most satisfactorily. According to this theory transition state is stabilized by electron donation from the anti-periplanar donor bonds into the σ^* orbital of the forming bond. Since the σ^* orbital develops on the same side irrespective of which partner brings the bonding electrons, the directional preference remains unaltered for both nucleophilic and electrophilic additions.

The ongoing debate concerning the role of electrostatic effects in controlling the face-selectivities and demonstration of its competition with orbital effects, promoted us to design new experiments using 7-isopropylidenenorbornane derivatives as probes. The electrophilic additions to 154a,b with CCl_2, Br^+, $^1O_2$ and per-acid gave products derived from the predominant syn-approach of the reagents indicating that even a single electron withdrawing group such as CN or COOMe is capable of inducing facial discrimination in these systems. Unlike in 7-methylenenorbornane derivatives, here there is no mechanistic ambiguity about the site of attack and the approach of the reagents, particularly for charged electrophiles (in this case Br^+). A topographical analysis of the MESP's of 154a,b at ab initio level with 6-31G basis set revealed that the MESP's are unsymmetrical about the two π-faces with greater concentration of electron density on the anti-face. However, this electron density on the anti-face was found to be significantly less-than that obtained for a typical C=C bond, a minimum threshold value, for orbital effects to play a role. Further calculations on the electron densities at bond central points in the systems 154a,b with electron withdrawing groups revealed that σ_a (C_1-C_6) bond consistently has greater density and hence Cieplak type orbital interaction are responsible for the observed syn-face selectivity.

The demonstration of homoconjugative interaction in 7-alkenyl norbornenes and intriguing results of electrophilic

additions to parent 7-isopropylidene norbornene led us to investigate the substituent effect in these systems too. The electrophilic additions to 152a,b with CCl_2, $^1O_2$ and per-acid demonstrate that the electron withdrawing groups indeed tilt the balance in favor of syn-addition (with respect to substituent) compared to the parent 7-isopropylidenenorbornene in each case. Although the reagent specific electrostatic effects have been proposed to account for the variation in the predominant approach of different electrophiles to parent 152 (R=H), the MESP's of 152a,b show that electrostatic effects are not important, even though MESP's are unsymmetrical about the two π-faces. The MESP's for 152a,b does indeed show visual homoconjugation between endocyclic and the bridged olefins, but the electron withdrawing groups (CN and COOMe) drain the electron density significantly from that face making it much less than the minimum threshold value required for electrostatics to play any role. The densities at bond central points in these systems reveal that an electron withdrawing substituent at C_5 increases the density at the C_3-C_4 bond (σ_a) relative to that at the C_4-C_5 (σ_s) bond and hence should favor electrophilic attack from the syn-face (with respect to substituent) on the basis of the Cieplak hyperconjugative model.

The results enumerated above constitute an important body of experimental data on the origin of π-facial diastereoselection in view of the conflicting theories and current controversy. Our efforts provide a better under-

standing of the interplay of various factors such as steric, electronic and electrostatic in determining the origin of π-face selectivities. We hope that these results will stimulate others[70] in designing and studying newer systems to test our mechanistic findings and interpretations.

IV. EXPERIMENTAL

III. EXPERIMENTAL

Melting points : Melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected.

Infrared spectra : Infrared spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometers. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. All the samples were recorded either neat or as KBr wafers.

Nuclear magnetic specra : Proton (100 MHz) and carbon-13 (25 MHz) magnetic resonance spectra were recorded on JEOL FX-100 spectrometer unless mentioned otherwise. ^{1}H and ^{13}C-NMR samples were made in chloroform-d solvent and chemical shifts are reported in δ scale using tetramethylsilane (Me_4Si) as the internal standard. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. ^{13}C-NMR assignments differing by only 1-2 ppm can in some cases be interchanged.

Mass spectra : Mass measurements were carried-out on JEOL, JMS DX-303 spectrometer.

Elemental analysis: Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyzer.

Chromatography : Analytical thin-layer chromatographies

(tlc) were performed on (10 x 5 cm) glass plates coated (250 mμ) with Acme's Silica gel G or GF_{254} (containing 13% of calcium sulphate as binder). Visualization of the spots on tlc plates was achieved either by exposure to iodine vapour or by spraying sulfuric acid and heating the plates at 120°C. Column chromatography was performed using Acme's silica gel (100-200 mesh) and the column was usually eluted with ethyl acetate-hexane.

General : All reactions were monitored by employing tlc technique. Moisture-sensitive reactions were carried out by using standard syringe-septum techniques. Dichloromethane was distilled over P_2O_5. Benzene was distilled over sodium and stored over pressed sodium wire. Dry ether and dry THF were made by distilling them from sodium-benzophenone ketyl.

All solvent extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure on a Buchi-El rotary evaporator. Yields reported are isolated yields of material judged homogeneous by tlc and NMR spectroscopy.

7,7-Dimethoxy-1,4,5,6-tetrachloro bicyclo[2.2.1]hept-5-ene-2,3-endo,endo-dicarboxylic acid anhydride (48):[31]

A solution containing 53 g of 1,2,3,4-tetrachloro-5,5-dimethoxy cyclopentadiene, 19 g of maleic anhydride and 300 ml of dry xylene was refluxed for 1.25 h. On cooling, a white solid crystallised which was filtered and washed with pet.ether to furnish 48 (62 g, 86%).

mp. : 194-195°C (Lit.[31] 192°C)

7,7-Dimethoxybicyclo[2.2.1]hept-5-ene-2,3-endo,endo-dicarboxylic acid anhydride (49):

In a 500 ml two-necked R.B. flask fitted with a condenser, KOH guard tube and a septum, 300 ml of liq.NH_3 was taken and a solution of 48 (5 g, 0.014 mol) in 10 ml of dry THF and 3.2 ml of dry EtOH was added. Small pieces of freshly cut sodium were introduced to the reaction mixture with stirring till the blue colour persisted. The reaction mixture was stirred for another 20 min and 1-2 g of solid NH_4Cl was added. NH_3 was allowed to evaporate and crushed ice was added to the residue and the solution was acidified (~pH 2) with 50% aq.HCl. It was then extracted several times with ethyl acetate. The combined organic layer was washed with water. Removal of solvent and crystallisation furnished 49 (1 g, 30%).

mp. : 122°C

IR : 2975, 1860, 1780, 1100, 920 cm^{-1}

^1H NMR : δ 6.28 (2H, dd, $J_1 = J_2 = 2$ Hz), 3.64 (2H, m),

3.44 (2H, m), 3.23 (3H, s, -OMe), 3.17 (3H, s, -OMe).

^{13}C NMR : δ 171.42, 133.06, 121.30, 52.29, 50.00, 47.53, 44.59.

7,7-Dimethoxybicyclo[2.2.1]heptane-2,3-endo,endo-dicarboxylic acid anhydride (50):

A solution of unsaturated anhydride 49 (1 g, 4.46 mmol) in 5 ml dry of ethyl acetate was hydrogenated at 20 psi over 10% Pd/C (10 mg) for a period of 20-30 min. The catalyst was filtered and the solvent removed to furnish the saturated anhydride 50 (0.96 g, 95%) which was recrystallised from dichloromethane-hexane.

mp. : 125°C

IR : 2950, 1860, 1780, 1230, 1080, 920 cm^{-1}

^{1}H NMR : δ 3.46 (2H, br s), 3.24 (6H, s, -OMe), 2.56 (2H, br s), 1.90 (2H, 1/2 ABq, J = 8 Hz), 1.36 (2H, 1/2 ABq, J = 8 Hz).

^{13}C NMR : δ 172.59, 115.59, 50.82, 47.06, 40.70, 22.53.

Analysis : $C_{11}H_{14}O_5$: Calcd. : C, 58.40; H, 6.24
Found : C, 58.49; H, 6.26.

Dimethyl 7,7-dimethoxybicyclo[2.2.1]heptane-2,3-endo,endo-dicarboxylate (51):

In a 250 ml R.B. flask with a condenser was placed a solution of anhydride 50 (1.5 g, 6.64 mmol) in dry methanol (100 ml) and 4-5 drops of conc.H_2SO_4 were carefully added. The reaction mixture was refluxed for 4-5 h. Excess

methanol was then removed under vacuum and water (10 ml) was added. The aqueous layer was extracted thrice with ethyl acetate and the combined organic layers were washed and dried. Removal of solvent and filteration of the residue through a silica gel column furnished 51 (1.26 g, 70%).

bp. : 110-120°C/0.3 mm

IR : 2950, 1735, 1200, 1060 cm^{-1}

^1H NMR : δ 3.64 (6H, s, -COOMe), 3.26 (8H, s), 2.32 (2H, br s, bridgehead CH), 1.75 (4H, m)

^{13}C NMR : δ 172.95, 112.88, 51.41, 50.65, 50.41, 43.94, 41.29, 21.58

Dimethyl bicyclo[2.2.1]heptan-7-one-2,3-endo,endo-dicarboxylate (47a):

To a solution of 51 (1 g, 3.68 mmol) in THF (5 ml), 5% H_2SO_4 (20 ml) was added. The reaction mixture was gently refluxed for 1.5 h. It was cooled and saturated with solid NaCl and extracted with ethyl acetate. The organic layer was washed and dried. After removal of solvent, the residue was charged on a silica gel column. Elution with 50% ethyl acetate-hexane furnished the ketone 47a (598 mg, 72%) as a low melting solid which showed very high propensity to form a hydrate.

mp. : 42-45°C

IR : 2950, 1770, 1730, 1200 cm^{-1}

^1H NMR : δ 3.70 (6H, s, -COOMe), 3.26 (2H, br s, >CHCOOMe), 2.28 (2H, br s, bridgehead CH), 2.20-1.60 (4H, series of m)

^{13}C NMR : δ 210.48, 171.24, 52.00, 42.06, 40.53, 18.41.

5,6-endo,endo-Bis(hydroxymethyl)-7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (52):

To a solution of 48 (20 g, 55.5 mmol) in methanol (80 ml) conc.H_2SO_4 (10-12 drops) was added and the reaction mixture was refluxed for 48 h. A white solid separated out on cooling which was filtered and recrystallized from methanol (16 g, 70%).

mp. : 103-104°C (Lit.[33] 103-104°C)

To a suspension of $LiAlH_4$ (1.86 g, 49.0 mmol) in 100 ml of dry ether was added the above diester (10 g, 24.51 mmol) in 200 ml of ether and the mixture stirred overnight. excess $LiAlH_4$ was destroyed by carefully adding few drops of ethyl acetate to the cooled reaction mixture. A saturated solution of Na_2SO_4 was added dropwise with stirring till a granular precipitate was formed. The precipitate was filtered and washed thoroughly with ethyl acetate. The filterate and the ethyl acetate washings were combined, washed and dried. Removal of solvent afforded 52 (6.04 g, 70%) as a solid residue. A small portion of the crude sample was recrystallised from dichloromethane-hexane.

mp. : 139-140°C (Lit.[34] 144-145°C)

5,6-endo,endo-Bis(hydroxymethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-2-ene (53):

Liquid NH_3 was placed in a 500 ml two necked R.B. flask fitted with a condenser, KOH guard tube and a septum and a

solution of 52 (5 g, 14.2 mmol) in dry THF (10 ml) was added with the help of a syringe. Small pieces of freshly cut sodium were added to the reaction mixture with stirring till the blue colour persisted. The reaction mixture was stirred for another 20 min and 4-5 ml of ethanol was added. NH_3 was allowed to evaporate and crushed ice was added to the residue which was acidified (~pH 2) with 50% HCl. The aqueous layer was extracted several times with ethyl acetate. The combined organic layers were washed with water and dried. The solvent was evaporated and the residue was charged on a silica gel column. Elution with ethyl acetate gave the diol 53 (2.13 g, 70%).

IR : 3350, 2950, 1300, 1050 cm^{-1}

^1H NMR : δ 6.07 (2H, dd, $J_1 = J_2 = 2.2$ Hz, olefnic), 4.10 (2H, br s, -OH, exchangeable with D_2O), 3.67-3.40 (4H, series of m, $-CH_2OH$), 3.24 (3H, s -OMe), 3.13 (3H, s, -OMe), 2.85 (2H, m), 2.81-2.69 (2H, m).

^{13}C NMR : δ 132.30, 118.41, 62.35, 51.88, 49.82, 48.76, 42.88.

Analysis : $C_{11}H_{18}O_4$: Calcd. : C, 61.66; H, 8.47
Found : C, 61.65; H, 8.49.

2,3-endo,endo-Bis(hydroxymethyl)-7,7-dimethoxybicyclo-[2.2.1]heptane (54):

A solution of the unsaturated diol 53 (2 g, 9.26 mmol) in 4 ml of dry ethyl acetate was shaken in a Parr hydrogenation apparatus over 10% Pd/C (30 mg) at a hydrogen pressure

of 20 psi. After 30 min the catalyst was filtered off and solvent removed to furnsih the saturated diol 54 (2 g, 100%).

mp. : 84-85°C

IR : 3200, 2900, 1200, 1060, 1010 cm^{-1}

^1H NMR : δ 4.02 (2H, m, $C\underline{H}_2OH$), 3.63 (2H, dd, J_1 = 3 Hz, J_2 = 11 Hz, $-C\underline{H}_2OH$), 3.31 (3H, s, $-O\underline{Me}$), 3.26 (3H, s, $-O\underline{Me}$), 2.97(2H, br s, $-O\underline{H}$, exchangeable with D_2O), 2.51 (2H, m), 2.09 (2H, m),1.70-1.51 (2H, m), 1.42-1.28 (2H, m)

^{13}C NMR : δ 112.76, 61.05, 50.37, 50.02, 41.39, 40.15, 20.31.

Analysis : $C_{11}H_{20}O_4$: Calcd. : C, 61.09; H, 9.32
Found : C, 60.71; H, 9.55.

2,3-endo,endo-Bis(methoxymethyl)-7,7-dimethoxybicyclo-[2.2.1]heptane (55):

To a suspension of NaH (197 mg, 60%, 4.92 mmol) in dry THF (1 ml), a solution of 54 (443 mg, 2.05 mmol) in THF (2 ml) was added under N_2 blanket. The mixture was stirred for 20 min at room temperature during which time a white slurry was formed. To this slurry CH_3I (700 mg, 4.92 mmol) in dry THF (1 ml) was added and the mixture was stirred at room temperature for another 20 min. Brine was added and the aqueous layer was extracted with ethyl acetate. Removal of solvent and column purification using silica gel furnished 55 as an oil (400 mg, 80%).

IR : 2900, 1460, 1320, 1200, 1100 cm^{-1}

^{1}H NMR : δ 3.60-3.20 (4H, series of m, $-C\underline{H}_2OMe$), 3.30 (6H, s, $-CH_2O\underline{Me}$), 3.26 (3H, s, $-O\underline{Me}$), 3.24 (3H, s, $-O\underline{Me}$), 2.48 (2H, m), 2.06 (2H, br s), 1.72-1.28 (4H, m).

^{13}C NMR : δ 113.35, 70.35, 58.71, 50.47, 50.12, 40.70, 37.00, 20.00.

2,3-endo,endo-Bis(methoxymethyl)bicyclo[2.2.1]heptan-7-one (47b):

A mixture of 55 (300 mg, 1.23 mmol) and amberlyst-15 (50-100 mg) in moist acetone (5 ml) was refluxed for 1.5 h. The resin was filtered and the solvent was removed to furnish a residue which was charged on a silica gel column. Elution with 30% ethyl acetate-hexane furnished 47b (170 mg, 70%).

IR : 2900, 1780, 1460, 1100, 960 cm^{-1}

^{1}H NMR : δ 3.52 (4H, m, $-C\underline{H}_2OMe$), 3.30 (6H, s, $-CH_2O\underline{Me}$), 2.50 (2H, m), 1.98 (2H, m), 1.75 (4H, br s).

^{13}C NMR : δ 215.13, 66.88, 58.76, 42.12, 34.23, 16.76.

HRMS : $C_{11}H_{18}O_3$: Calcd. : 198.1256
Found : 198.1256.

2-endo-[(tert-Butyldimethylsiloxy)methyl]-3-endo-hydroxymethyl-7,7-dimethoxy bicyclo[2.2.1]heptane (56):

NaH (229 mg, 60%, 5.7 mmol) was suspended in THF (2 ml) in a R.B. flask fitted with a condenser and a septum. The diol 54 (1.12 g, 5.19 mmol) in THF (4 ml) was added at room temperature and the mixture stirred for 20 min at which time a large amount of opaque white precipitate had formed. The

TBDMSCl (785 mg, 5.19 mmol) in THF was then added and vigorous stirring was continued for 45 min. The reaction was quenched with 10% K_2CO_3 and extracted thrice with ethyl acetate. The combined organic layers were washed with 10% K_2CO_3, water and dried. Removal of solvent and column purification using silica gel furnished 56 (1.37 g, 80%).

bp. : 100-110°C/0.3 mm

IR : 3400, 2950, 1060, 840 cm^{-1}

^1H NMR : δ 4.02-3.70 (2H, m), 3.68-3.30 (2H, m), 3.20 (3H, s, -OMe), 3.14 (3H, s, -OMe), 2.48-2.20 (2H, m), 1.97 (2H, br s), 1.60-1.10 (4H, series of m), 0.80 (9H, s, $-CMe_3$), 0.00 (6H, s, $>SiMe_2$).

^{13}C NMR : δ 112.83, 62.29, 60.88, 50.35, 49.94, 41.35, 40.47, 40.17, 25.70, 20.17, 18.00, -5.49

2-endo-[(tert-Butyldimethylsiloxy)methyl]-3-endo-ethenyl-7,7-dimethoxy bicyclo[2.2.1]heptane (57):[37]

To oxalyl chloride (2.88 ml, 22.23 mmol) in dichloromethane (5 ml) was added DMSO (4.76 ml, 67.1 mmol) in CH_2Cl_2 (5 ml) at -60°C. After the mixture was stirred for 15 min. at -60°C, the alcohol 56 (4.5 g, 13.62 mmol) in CH_2Cl_2 (10 ml) was added and stirred for 15 min. Finally triethylamine (16 ml, 114.8 mmol) was added, and the reaction mixture was stirred for 5 min. at -60°C and then warmed to 0°C. At 0°C, water (20 ml) was added and stirring was continued for another 10 min. The reaction mixture was diluted with CH_2Cl_2, washed with water and dried. Evaporation of the

solvent afforded crude aldehyde as an yellow oil.

To a suspension of methyltriphenylphosphoniumbromide (7.29 g, 20.43 mmol) in dry benzene (20 ml) was added freshly sublimed sodium t-amyl oxide (1.52 g, 13.78 mmol) in benzene (15 ml) and the mixture stirred for 5 min at room temperature. To the canary yellow ylide that formed immediately was added the above aldehyde in benzene (5 ml) and the reaction mixture was stirred further for 15 min and quenched with water (20 ml). The benzene layer was separated and the aqueous layer extracted with benzene. The combined organic layer was washed and dried. After the removal of solvent, the residue was charged on silica gel column. Elution with 5% ethyl acetate-hexane furnished 57 (2.67 g, 60%).

bp. : 120-130°C/0.3 mm

IR : 2900, 1100, 1070, 840 cm^{-1}

^1H NMR : δ 6.06-5.64 (1H, m, $-C\underline{H}=CH_2$), 5.16-4.90 (2H, m, $-CH=C\underline{H}_2$), 3.56 (2H, d, J = 8 Hz, $-C\underline{H}_2-SiMe_2-$), 3.28 (3H, s, $-O\underline{Me}$), 3.26 (3H, s, $-O\underline{Me}$), 3.00-2.68 (1H, m), 2.58-2.20 (1H, m), 2.14 (1H, br s, bridgehead C<u>H</u>), 1.96 (1H, br s, bridgehead C<u>H</u>), 1.60 (4H, br s, $\underline{H}_{5,6}$), 0.84 (9H, s, $-C\underline{Me}_3$), 0.02 (6H, s, $>Si\underline{Me}_2$).

^{13}C NMR : δ 143.59, 114.41, 112.00, 62.88, 50.12, 46.41, 44.12, 39.76, 28.35, 25.88, 19.64, 18.17, -5.19.

2-endo-Ethenyl-3-endo-hydroxymethyl-7,7-dimethoxybicyclo-[2.2.1]heptane (58):

To a solution of olefin 57 (2.3 g, 7.04 mmol) in THF (6 ml) was added tert-butylammonium fluoride (2.21 g, 8.45 mmol). The reaction was stirred at room temperature for 1 h, diluted with ethyl acetate, washed with 10% K_2CO_3 and dried. Solvent was evaporated and the residue was charged on a silica gel column. Elution with 20% ethyl acetate hexane furnished 58 (1.4 g, 94%).

bp. : 110-120°C/0.3 mm

IR : 3350, 3050, 2950, 1200, 1060 cm^{-1}

^1H NMR : δ 6.08-5.68 (1H, m, -CH=CH_2), 5.16-4.90 (2H, m, -CH=CH_2), 3.74-3.34 (2H, m, -CH_2OH), 3.23 (3H, s, -OMe), 3.20 (3H, s, -OMe), 3.00-2.68 (1H, m), 2.54-2.22 (1H, m), 2.06 (1H, br s, bridgehead CH), 1.96 (1H, br s, bridgehead CH), 1.54 (br s, $H_{5,6}$).

^{13}C NMR : δ 136.59, 118.00, 113.59, 61.12, 50.47, 50.18, 44.00, 42.41, 41.87, 40.12, 20.41, 20.06.

Analysis : $C_{12}H_{20}O_3$: Calcd. : C, 67.89; H, 9.50
Found : C, 67.95; H, 9.53.

2,3-endo,endo-Diethenyl-7,7-dimethoxybicyclo[2.2.1]heptane (59):

The Swern oxidation of alcohol 58 (700 mg, 3.3 mmol) followed by Wittig olefination of the resulting aldehyde were carried out as described above for 57. After the usual work-up, the residue was charged on a silica gel column.

Elution with 3% ethyl acetate-hexane furnished the divinyl compound 59 (350 mg, 51%) which was found to be a mixture of endo, endo- and endo,exo-isomers (^{1}H NMR). The mixture contained about 25-30% endo, exo-isomer. The two isomers were separated by column chromatography using $AgNO_3$ impregnated silica gel. On elution with 3% ethyl acetate-hexane, the endo, exo-isomer eluted out first. Further elution of the column furnished the required endo,endo-isomer 59.

IR : 3050, 2950, 1120, 1060, 910 cm^{-1}

^{1}H NMR : δ 6.00-5.60 (2H, m, -C<u>H</u>=CH_2), 5.04-4.76 (4H, m, -CH=C<u>H</u>$_2$), 3.24 (3H, s, -O<u>Me</u>), 3.20 (3H, s, -O<u>Me</u>), 2.96-2.78 (2H, m, >C<u>H</u>-CH=CH_2), 1.98 (2H, br s, bridgehead C<u>H</u>), 1.60 (4H, br s, <u>H</u>$_{5,6}$).

^{13}C NMR : δ 137.77, 116.53, 113.59, 50.47, 50.12, 44.47, 43.70, 20.53,

2,3-<u>endo</u>,<u>endo</u>-Diethenyl bicyclo[2.2.1]heptan-7-one (<u>47c</u>):

A solution of 59 (200 mg, 0.96 mmol) in moist acetone (5 ml) was refluxed with amberlyst-15 (50-100 mg) for 5-6 h. The resin was filtered off, solvent was removed and the residue was purified by column chromatography using silica gel to furnish 47c (94 mg, 60%).

IR : 3050, 2950, 1770, 910 cm^{-1}

^{1}H NMR : δ 6.14-5.74 (2H, m, -C<u>H</u>=CH_2), 5.24-4.92 (4H, m, -CH=C<u>H</u>$_2$), 2.98 (2H, m, >C<u>H</u>-CH=CH_2), 2.12-1.60 (6H, series of m).

^{13}C NMR : δ 215.07, 135.06, 118.36, 44.88, 41.35, 17.41.

HRMS : $C_{11}H_{14}O$: Calcd. : 162.1045
Found : 162.1033.

2-endo-Ethenyl-3-endo-ethyl-7,7-dimethoxy bicyclo[2.2.1]heptane (60):

A solution of the mono alcohol 58 (300 mg, 1.42 mmol) in dry ethyl acetate (2 ml) was shaken in a Parr hydrogenator over 10% Pd/C (5 mg) at a hydrogen pressure of 40 psi. After 45 min, the catalyst was filtered and solvent removed to furnsih the saturated alcohol (300 mg, 100%).

IR : 3400, 1320, 1200, 1140, 1060 cm^{-1}

^1H NMR : δ 3.84-3.52 (2H, m, $-C\underline{H}_2OH$), 3.31 (3H, s, $-O\underline{Me}$), 3.29 (3H, s, $-O\underline{Me}$), 2.50-1.90 (3H, m), 1.80-1.20 (7H, series of m), 0.80 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$).

The Swern oxidation of the above saturated alcohol (150 mg, 0.7 mmol) followed by Wittig olefination of the resulting aldehyde were carried out as described above for 57. After the usual work-up, the residue was charged on a silica gel column. Elution with hexane furnished 60 (88 mg, 60%).

IR : 3075, 2975, 1060, 910 cm^{-1}

^1H NMR : δ 6.16-5.74 (1H, m, $-C\underline{H}=CH_2$), 5.16-4.84 (2H, m, $-CH=C\underline{H}_2$), 3.30 (3H, s, $-O\underline{Me}$), 3.27 (3H, s, $-O\underline{Me}$), 2.96-2.64 (1H, m, $-C\underline{H}-CH=CH_2$), 2.20-1.76 (2H, m), 1.72-1.08 (7H, series of m), 0.78 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$).

^{13}C NMR : δ 138.06, 116.83, 113.77, 50.53, 50.18, 44.53,

43.76, 41.23, 40.82, 20.53, 20.35, 19.53, 13.23.

2-endo-Ethenyl-3-endo-ethyl bicyclo[2.2.1]heptan-7-one (47d):

A mixture of 60 (80 mg, 0.38 mmol) and amberlyst-15 (25 mg) in moist acetone (3 ml) was refluxed for 8 h. The resin was filtered and the solvent was removed. The residue was charged on a silica gel (5 g) column. Elution with 2% ethyl acetate-hexane furnished 47d (38 mg, 60%).

IR : 3050, 2950, 1760, 1140, 910 cm^{-1}

^1H NMR : δ 6.20-5.80 (1H, m, $-C\underline{H}=CH_2$), 5.22-4.96 (2H, m, $-CH=C\underline{H}_2$, 3.02-.270 (1H, m, $-C\underline{H}-CH=CH_2$), 2.36-2.04 (1H, m), 2.04-1.20 (8H, series of m), 0.82 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$).

^{13}C NMR : δ 216.18, 134.95, 118.65, 45.88, 42.35, 40.70, 38.70, 19.58, 17.41, 16.29, 13.00.

Mass (m/e) : 164 (M^+, 54), 135(72), 121(50), 107(95), 91(83), 79(95), 67(100).

2,3-endo,endo-Diethyl-7,7-dimethoxy bicyclo[2.2.1]heptane (61):

A solution of the divinyl compound 59 (105 mg, 0.5 ml) in dry ethyl acetate (3 ml) was shaken in a Parr hydrogenation apparatus over PtO_2 (3 mg) at a hydrogen pressure of 40 psi. After 30 min, the catalyst was filtered off and solvent removed to furnish the saturated diethyl derivative 61 (105 mg, 100%).

IR : 2950, 1200, 1080 cm^{-1}

^{1}H NMR : δ 3.27 (3H, s, -OMe), 3.26 (3H, s, -OMe), 1.96 (4H, m), 1.60-1.12 (8H, series of m), 0.76 (6H, t, J = 7 Hz, $-CH_2-CH_3$).

^{13}C NMR : δ 113.53, 50.29, 49.94, 40.65, 39.88, 19.23, 18.76, 13.11.

2,3-endo,endo-Diethyl bicyclo[2.2.1]heptan-7-one (47e):

A mixture of 61 (90 mg, 0.43 mmol) and amberlyst-15 (30 mg) in moist acetone (3 ml) was stirred at room temperature for 12 h. Amberlyst resin was filtered and the solvent was removed to furnish a residue which was charged on a silica gel column. Elution with 2% ethyl acetate hexane furnished 47e (57 mg, 80%).

IR : 2950, 1770, 1160 cm^{-1}

^{1}H NMR : δ 2.20-1.04 (12H, series of m), 0.76 (6H, t, J = 7 Hz, $-CH_2-CH_3$).

^{13}C NMR : δ 217.24, 42.41, 37.41, 17.82, 16.11, 12.88.

Mass (m/e) : 166 (M^+, 35%), 133 (100%), 109 (58%), 95(63%), 67(95%).

HRMS : $C_{11}H_{18}O$: Calcd. : 166.1357
Found : 166.1358.

$NaBH_4$ reduction of anhydride 50: Formation of lactone (62):

To a solution of anhydride 50 (3.8 g, 16.8 mmol) in dry THF (10 ml) at 0°C was added $NaBH_4$ (638 mg, 16.8 mmol) under N_2. The reaction mixture was stirred at 0-15°C for 45 min. The reaction was then carefully quenched at 0°C with 10% HCl and extracted thrice with ethyl acetate. After the removal

of solvent, the residue was charged on a silica gel column. Elution with 30% ethyl acetate-hexane afforded 62 (2.4 g, 67%).

mp. : 87-88°C

IR : 2975, 1780, 1200, 1140, 1080 cm^{-1}

^1H NMR : δ 4.44-4.16 (2H, m, -C<u>H</u>$_2$-OCO-), 3.28 (3H, s, -O<u>Me</u>), 3.27 (3H, s, -O<u>Me</u>), 3.10 (2H, m), 2.46 (1H, br s, bridgehead C<u>H</u>), 2.18 (1H, br s, bridgehead C<u>H</u>), 2.00-1.24 (4H, series of m, <u>H</u>$_{5,6}$).

^{13}C NMR : δ 178.65, 116.12, 68.18, 50.65, 44.53, 41.12, 40.53, 38.12, 22.76, 19.64.

Analysis : $C_{11}H_{16}O_4$: Calcd. : C, 62.25; H, 7.60
Found : C, 62.28; H, 7.58.

Lactol derivative (63):

To a solution of lactone 62 (1.4 g, 6.6 mmol) in dry CH_2Cl_2 at -78°C was added DIBAL-H (6.7 ml of 1.2 M solution in toluene, 7.92 mmol). The reaction mixture was stirred at -78°C for 15 min and quenched by careful addition of a few drops of methanol. The mixture was diluted with CH_2Cl_2, washed and dried. Removal of solvent gave the lactol 63 (1.1 g, 78%) which was directly used for the next step.

mp. : 92°C

IR : 3225, 2975, 1230, 1140, 1090 cm^{-1}

^1H NMR : δ 5.36 (1H, br s, >C<u>H</u>OH), 4.12-3.68 (2H, m, -CH_2-O-), 3.26 (6H, s, -O<u>Me</u>), 2.96-2.50 (2H, m), 2.21 (1H, m, bridgehead C<u>H</u>), 2.02 (1H, m,

bridgehead C<u>H</u>), 1.68-1.20 (4H, series of m, <u>H</u>$_{5,6}$).

^{13}C NMR : δ 117.18, 99.06, 66.47, 50.53, 50.29, 41.35, 41.23, 40.06, 21.23, 20.23.

Analysis : $C_{11}H_{18}O_4$: Calcd. : C, 61.66; H, 8.47
Found : C, 61.60; H, 8.45.

2-<u>endo</u>-Ethenyl-3-<u>endo</u>-hydroxymethyl-7,7-dimethoxybicyclo-[2.2.1]heptane (<u>58</u>):

To a suspension of methyltriphenylphosphonium bromide (7.3 g, 20.45 mmol) in dry benzene (22 ml) was added freshly sublimed sodium t-amyloxide (1.7 g, 15.46 mmol) in benzene (10 ml) and the mixture stirred for 5 min at room temperature. To the canary yellow ylide that formed immediately was added the lactol <u>63</u> (1.1 g, 5.14 mmol) and the reaction mixture stirred further for 30 min and quenched with water (15 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed and dried. The solvent was evaporated and the residue charged on a silica gel column. Elution with 25% ethyl acetate-hexane furnished <u>58</u> (0.77 g, 71%).

Bromoetherification of <u>endo</u>, <u>endo</u>-diol (<u>53</u>):

To a solution of diol <u>53</u> (2.5 g, 11.68 mmol) in moist acetone (10 ml) was added NBS (2.3 g, 12.92 mmol) and the reaction mixture stirred overnight at room temperature. Removal of solvent under reduced pressure furnished a residue which was directly charged on a neutral alumina

column (40 g). Elution with ethyl acetate furnished 78 (3.15 g, 92%).

IR : 3350, 2900, 1140, 1060, 730 cm^{-1}

^1H NMR : δ 4.62 (1H, d, J = 5 Hz), 3.88-3.50 (5H, m), 3.34 (3H, s, -OMe), 3.29 (3H, s, -OMe), 2.94-2.48 (3H, series of m), 2.46 (1H, m).

^{13}C NMR : δ 112.47, 88.35, 68.77, 59.29, 51.00, 50.47, 50.35, 50.23, 45.00, 41.59, 36.82.

10,10-Dimethoxy-2,7-dioxatetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]-undecane (79):

In a 25 ml two necked R.B. flask equipped with a dry nitrogen inlet was placed NaH (345 mg, 60% wt. dispersion in oil, 8.60 mmol) in dry THF (3 ml). A solution of the alcohol 78 (2.1 g, 7.17 mmol) in dry THF (5 ml) was added dropwise at room temperature. The reaction mixture was refluxed for 2 h and then diluted with brine and extracted with ethyl acetate (3 x 50 ml). The combined organic extract was washed and dried. Removal of solvent gave a crude material which was charged on a silica gel (30 g) column. Elution with 50% ethyl acetate-hexane furnished 79 (1g, 66%).

mp. : 126°C

IR : 2950, 1340, 1070, 1050 cm^{-1}

^1H NMR : δ 4.16 (2H, br s, >CH-O-), 4.10 (2H, d, J = 9 Hz, $-CH_2O-$), 3.71 (2H, d, J = 9 Hz, $-CH_2O-$), 3.34 (3H, s, -OMe), 3.28 (3H, s, -OMe), 2.65 (4H, m).

^{13}C NMR : δ 107.00, 77.94, 69.29, 50.76, 50.35, 48.18, 39.94.

Analysis : $C_{11}H_{16}O_4$: Calcd. : C, 62.25; H, 7.60
Found : C, 62.15; H, 7.65.

2,7-Dioxatetracyclo[6.3.0.$0^{4,11}0^{5,9}$]undecan-10-one (77a):

A mixture of ketal 79 (312 mg, 1.47 mmol) and amberlyst-15 (50 mg) in moist acetone (4 ml) was refluxed for 30 min. Amberlyst resin was filtered and the solvent was removed The residue was purified by successively passing it through neutral alumina (elution with 5% methanol-ethyl acetate) and silica gel (elution with ethyl acetate) columns to obtain 77a (198 mg, 81%).

mp. : 177-178°C

IR : 2950, 1770, 1390, 1070, 1010 cm^{-1}

^1H NMR : δ 4.46 (2H, d, J = 2.2 Hz, >C<u>H</u>-O), 4.38 (2H, d, J = 9.2 Hz, -C<u>H</u>$_2$O-), 3.78 (2H, dd, J_1 = 9.2 Hz, J_2 = 1.6 Hz, -C<u>H</u>$_2$-O-), 2.99 (2H, br s), 2.43 (2H, m).

^{13}C NMR : δ 208.42, 77.12, 69.24, 48.59, 38.65.

Analysis : $C_9H_{10}O_3$: Calcd.: C, 65.05; H, 6.07 for ketone &
C, 58.69; H, 6.57 for hydrate
Found : C, 58.48; H, 6.62.

7,7-Dimethoxy-2-oxatricyclo[4.2.1.$0^{4,8}$]nonane (81):

A mixture of alcohol 80 (500 mg, 2.72 mmol) and $Hg(OAc)_2$ (1.1 g, 3.45 mmol) in 1:1 water-THF (8 ml) was stirred at room temperature for 20 min. At this stage 3 M

NaOH solution (10 ml) was added followed by 0.5M $NaBH_4$ solution in 3M NaOH (10 ml). The reaction mixture was stirred further for 30 min. It was then saturated with solid NaCl and extracted thrice with ethyl acetate. The organic layer was washed and dried. Removal of solvent and column purification using silica gel (15 g) furnished 81 (363 g, 73%).

IR : 2950, 1340, 1120, 1060 cm^{-1}

^1H NMR : δ 4.42 (1H, dd, $J_1 = J_2 = 6$ Hz), 3.83 (1H, d of 1/2 ABq, $J_1 = 8$ Hz, $J_2 = 4$ Hz, $-C\underline{H_2}-O-$), 3.71 (1H, 1/2 ABq, $J_1 = 8$ Hz, $-C\underline{H_2}-O-$), 3.30 (3H, s, $-O\underline{Me}$), 3.24 (3H, s, $-O\underline{Me}$), 2.62-2.46 (2H, m), 2.37-2.21 (1H, m), 2.14-1.98 (2H, m), 1.22-1.09 (2H, m).

^{13}C NMR : δ 115.24, 78.71, 74.82, 50.47(2C), 48.65, 38.12, 37.06, 36.23, 36.06.

Analysis : $C_{10}H_{16}O_3$: Calcd. : C, 65.19; H, 8.75
Found : C, 65.25; H, 8.72.

2-Oxatricyclo[4.2.1.$0^{4,8}$]nonan-7-one (77b):

A mixture of ketal 81 (300 mg, 2.17 mmol) and amberlyst-15 (50 mg) in moist acetone (4 ml) was stirred at room temperature for 6 h. Amberlyst resin was filtered and the solvent was removed. The residue was purified by passing it successively through silica gel (elution with 15% ethyl acetate-hexane) and neutral alumina (elution with ethyl acetate) columns to obtain 77b (126 mg, 56%).

mp. : low melting waxy solid

IR : 2925, 1760, 1130, 1000 cm^{-1}

^{1}H NMR : δ 4.59 (1H, dd, $J_1 = J_2 = 5.4$ Hz, >C<u>H</u>-O-), 3.92 (1H, d of 1/2 ABq, $J_1 = 8$ Hz, $J_2 = 4$ Hz, -C<u>H</u>$_2$-O-), 3.87 (1H, 1/2 ABq, $J_1 = 8$ Hz), 2.80-2.68 (1H, m), 2.43 (1H, dd, $J_1 = J_2 = 5$ Hz), 2.39-2.22 (1H, m), 2.15-2.00 (2H, m), 1.53 (1H, dd, $J_1 = 12.6$ Hz, $J_2 = 2$ Hz), 1.41 (1H, dd, $J_1 = 12.6$ Hz, $J_2 = 2$ Hz).

^{13}C NMR : δ 213.07, 75.59, 75.35, 48.00, 38.17, 35.82, 35.17, 31.82.

Analysis : $C_8H_{10}O_2$: Calcd. : C, 69.54; H, 7.30
Found : C, 69.45; H, 7.28.

7,7-Dimethoxy-2-oxatricyclo[4.2.1.0^{4,8}]nonan-3-one <u>82</u>:

To an yellow coloured solution of $Hg(OAc)_2$ (1.08 g, 3.39 mmol) in 1:1 water-THF was added the acid <u>83</u> (560 mg, 2.83 mmol) and the yellow colour discharged immediately. The mixture was stirred at room temperature for 20 min. At this stage, 3 M NaOH solution (2.8 ml) was added followed by the addition of a solution of 0.5 M $NaBH_4$ in 3 M NaOH (2.8 ml) and the mixture was stirred further for 20 min. Crushed ice was added and the mixture was acidified (~pH 2) with 20% HCl. It was then saturated with solid NaCl and extracted thrice with ethyl acetate. The organic layer was washed and dried. Removal of solvent and column purification using neutral alumina (20 g) furnished <u>82</u> (400 mg, 71%).

Ruthenium (VIII) catalyzed oxidation of <u>81</u>:

A reaction mixture containing the ether <u>81</u> (75 mg, 0.41 mmol), $RuCl_3.3H_2O$ (5 mg) and sodium metaperiodate (150 mg,

0.70 mmol) in a solvent mixture (2 ml CCl_4, 1 ml acetonitrile and 3 ml water) was stirred vigorously at reflux temperature for 3-4 h. The reaction mixture was worked-up by separating the organic layer and extracting the aqueous layer with dichloromethane (3 x 10 ml). The combined organic phase was washed and dried. Removal of solvent and column purification on silica gel (elution with 25% ethyl acetate-hexane) furnished the lactone 82 (69 mg, 86%).

mp. : 60-61°C

IR : 2950, 1770, 1190, 1130, 1080 cm^{-1}

^1H NMR : δ 4.83 (1H, dd, $J_1 = J_2 = 6$ Hz, >CHOCO-), 3.29 (3H, s, -OMe), 3.27 (3H, s, -OMe), 3.12 (1H, dt, $J_1 = 5$ Hz, $J_2 = 1$ Hz), 2.73-2.63 (1H, m), 2.43-2.14 (3H, series of m), 1.76 (1H, d, J = 13 Hz), 1.54 (1H, d, J = 13 Hz).

^{13}C NMR : δ 180.47, 114.35, 79.47, 50.82(2C), 48.17, 38.70, 37.87, 35.46, 31.58.

Analysis : $C_{10}H_{14}O_4$: Calcd. : C, 60.59; H, 7.12
Found : C, 60.52; H, 7.14.

2-Oxatricyclo[4.2.1.$0^{4,8}$]nonan-3,7-dione (82):

To a cooled solution of lactone ketal 82 (100 mg, 0.51 mmol) in dry dichloromethane (4 ml) was added one drop of conc.H_2SO_4 with a capillary. The reaction mixture was allowed to warm to room temperature slowly and stirred for 4 h. It was diluted with dichloromethane, washed and dried. Solvent was removed and the residue was purified by column chromatography using silica gel (10 g, elution with 30%

ethyl acetate hexane). It was further purified by sublimation (200°C/atm. pressure) to furnish 77c (31 mg, 40%). The norbornane derivative 77c shows high tendency form a hydrate.

mp. : 120-160°C (sublimes)

IR : 2950, 1760, 1350, 1180, 1100, 980 cm^{-1}

^1H NMR : δ 5.02 (1H, dd, $J_1 = J_2 = 6$ Hz, >CH-OCO-), 3.03 (1H, dd, $J_1 = J_2 = 5$ Hz), 2.97-2.86 (1H, m), 2.41-2.20 (3H, series of m), 1.93 (2H, d, J = 14.4 Hz).

^{13}C NMR : δ 208.83, 178.77, 74.82, 47.18, 39.47, 35.00, 33.64, 26.59.

Analysis : $C_8H_8O_3$: Calcd. : C, 63.15; H, 5.30
Found : C, 63.10; H, 5.34.

Dimethyl-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-endo, endo-dicarboxylate (92):

In a 250 ml R.B. flask with a condenser was placed a solution of anhydride 49 (1 g, 4.46 mmol) in dry methanol (100 ml) and 4-5 drops of conc.H_2SO_4 were added carefully. The reaction mixture was refluxed for 4-5 h. Excess methanol was then removed under vacuum and water (10 ml) was added. The aqueous layer was extracted with ethyl acetate (3 x 25 ml) and the combined organic layer was washed and dried. Removal of solvent and filteration of the residue through a silica gel column furnished 92 (1.04 g, 86%).

mp. : 57-58°C

IR : 3050, 2950, 1730, 1280 1200, 1070 cm^{-1}

^{1}H NMR : δ 6.20 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.54 (6H, s, -COO<u>Me</u>), 3.42 (2H, m), 3.16 (3H, s, -O<u>Me</u>), 3.09 (5H, s).

^{13}C NMR : δ 172.48, 132.36, 117.24, 52.00, 51.53, 49.82, 48.29, 45.94.

Analysis : $C_{13}H_{18}O_6$: Calcd. : C, 57.77; H, 6.71
Found : C, 57.65; H, 6.65.

Dimethyl bicyclo[2.2.1]hept-5-ene-7-one-2,3-<u>endo</u>,<u>endo</u>-dicarboxylate (<u>91a</u>):

To a solution of <u>92</u> (1 g, 3.70 mmol) in THF (5 ml) was added 5% H_2SO_4 (20 ml) and the reaction mixture was refluxed gently for 30 min. The reaction mixture was cooled, saturated with solid NaCl and extracted with ethyl acetate (3 x 25 ml). The combined organic layer was washed with water and dried. Removal of solvent and column purification using silica gel (20 g, elution with 30% ethyl acetate-hexane) furnished enone <u>91a</u> (622 mg, 75%).

mp. : 84°C

IR : 2950, 1790, 1735, 1440, 1340, 1210, 1070 cm^{-1}

^{1}H NMR : δ 6.57 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.60 (6H, s, -COO<u>Me</u>), 3.44 (2H, m), 3.19 (2H, m).

^{13}C NMR : δ 198.30, 170.77, 131.30, 52.00, 49.65, 43.41.

Analysis : $C_{11}H_{12}O_5$: Calcd. : C, 58.92; H, 5.40
Found : C, 59.00; H, 5.41.

5,6-endo,endo-Bis(methoxymethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-2-ene (93):

In a 25 ml two necked R.B. flask equipped with a dry nitrogen inlet was placed NaH (387 mg, 9.65 mmol) in dry THF (2 ml). A solution of the diol 53 (860 mg, 4.02 mmol) in dry THF (2 ml) was added dropwise at room temperature. The mixture was stirred for 45 min during which time a white slurry was formed. To this slurry, CH_3I (1.37 g, 9.65 mmol) in dry THF (1 ml) was added and the mixture was stirred further for 45 min at room temperature. The reaction mixture was diluted with brine and extracted with ethyl acetate (3 x 30 ml). The combined organic extract was washed and dried. Removal of solvent gave a crude material which was charged on a silica gel column (20 g). Elution with 30% ethyl acetate-hexane furnished 93 (846 mg, 87%).

mp. : low melting

IR : 3050, 2900, 1280, 1090 cm^{-1}

^1H NMR : δ 6.16 (2H, dd, $J_1 = J_2 = 2.2$ Hz, olefinic), 3.29 (6H, s, $-CH_2O\underline{Me}$), 3.21 (3H, s, $-O\underline{Me}$), 3.13 (3H, s, $-O\underline{Me}$), 3.21-3.01 (4H, m, $-C\underline{H}_2OMe$), 2.97-2.92 (2H, m), 2.74-2.64 (2H, m).

5,6-endo,endo-Bis(methoxymethyl)bicyclo[2.2.1]hept-2-ene-7-one (91b):

A mixture of ketal 93 (400 mg, 1.65 mmol) and amberlyst-15 (50 mg) in moist acetone (5 ml) was refluxed for 30 min. Amberlyst resin was filtered and the solvent was removed. The residue was charged on a silica gel column

eluted with 30% ethyl acetate-hexane to furnished 91b (300 mg, 93%).

IR : 2900, 1770, 1100 cm^{-1}

^1H NMR : δ 6.49 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.29 (6H, s, $-CH_2O\underline{Me}$), 3.35-2.92 (6H, series of m), 2.78-2.52 (2H, m).

^{13}C NMR : δ 204.18, 131.83, 70.47, 58.71, 50.59, 37.29.

Analysis : $C_{11}H_{16}O_3$: Calcd. : C, 67.32; H, 8.22
Found : C, 67.28; H, 8.19.

5,6-endo,endo-Bis(hydroxymethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-2-ene diacetate (94):

To a solution of diol 53 (227 mg, 1.06 mmol) in dry dichloromethane (3 ml) at 0°C was added DMAP (260 mg, 2.13 mmol) and acetic anhydride (216 mg, 2.12 mmol). The reaction mixture was allowed to warm to room temperature slowly and stirred for 30 min. It was diluted with dichloromethane, washed and dried. Removal of solvent and column purification using silica gel (10 g, elution with 40% ethyl acetate-hexane) furnished the diacetate 94 (310 mg, 98%).

mp. : 88-89°C

IR : 3050, 2950, 1735, 1250, 1030 cm^{-1}

^1H NMR : δ 6.11 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.86-3.72 (4H, m, $-C\underline{H}_2OAc$), 3.16 (3H, s, $-O\underline{Me}$), 3.08 (3H, s, $-O\underline{Me}$), 2.87 (2H, br s), 2.68 (2H, m), 2.00 (6H, s, $-OCO\underline{Me}$).

^{13}C NMR : δ 170.81, 132.95, 118.12, 63.24, 51.76, 49.76, 48.00, 38.41, 20.82.

5,6-endo,endo-Bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene-7-one diacetate (91c):

A mixture of ketal 94 (200 mg, 0.67 mmol) and amberlyst-15 (50 mg) in moist acetone (4 ml) was refluxed for 8 h. The resin was filtered and the solvent was removed. The residue was charged on a silica gel column (10 g) and eluted with 50% ethyl acetate hexane to furnish the ketone 91c (101 mg, 60%).

mp. : 105-106°C

IR : 2950, 1780, 1730, 1250, 1040, 700 cm^{-1}

^1H NMR : δ 6.55 ((2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 4.14-3.70 (4H, m, $-CH_2OAc$), 3.06 (2H, br s), 2.78 (2H, m), 2.06 (6H, s, -OCOMe).

^{13}C NMR : δ 202.06, 170.77, 132.00, 62.18, 50.41, 36.70, 20.88.

7,7-Dimethoxy-1,4,5,6-tetrachloro bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (101):[59]

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene (10 g, 37.9 mmol), acrylic acid (2.73 g, 37.9 mmol) and a trace of hydroquinone were heated to 125-130°C for 45 min. The product was crystallised by adding hexane to the reaction mixture (11.96 g, 94).

mp. : 164-165°C (Lit.[59] 165-166°C)

Bicyclo[2.2.1]hept-5-ene-7-one-2-endo-carboxylic acid (102):[46b]

Liquid NH_3 (250 ml) was placed in a 500 ml two neck

R.B. flask equipped with a condenser and a KOH guard tube and the tetrachloro acid 101 (5 g, 14.9 mmol) in dry THF (3-4 ml) was added to it. Freshly cut sodium metal pieces were added slowly till the blue colour persisted. The reaction mixture was quenched with solid NH_4Cl after 30 min.

After evaporating NH_3 completely, 20% HCl was added to the reaction mixture (ca. pH~1). The reaction mixture was warmed on a water bath for 30 min. and saturated with solid NaCl. Extraction with hot ethyl acetate and crystallisation with hexane furnished 102 in 47% yield.

mp. : 102-103°C

IR : 3500-2400, 1770, 1690, 1260, 940 cm^{-1}

^1H NMR : δ 6.60 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 6.42 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.30-3.02 (2H, m, bridgehead CH; >CHCOOH), 2.96 (1H, dd, J_1 = J_2 = 4 Hz), bridgehead CH), 2.20 (1H, ddd, J_1 = 12 Hz, J_2 = 10 Hz, J_3 = 4 Hz, exo-H_3), 1.64 (1H, dd, J_1 = 12 Hz, J_2 = 5 Hz, endo-H_3).

^{13}C NMR : δ 202.13, 178.77, 134.77, 130.30, 48.36, 46.12, 38.00, 25.88.

Methyl bicyclo[2.2.1]hept-5-ene-7-one-2-endo-carboxylate (103b):

To a solution of 102 (1 g, 6.0 mmol) in dry ether (20 ml) was added an excess of ethereal solution of CH_2N_2 at 0°C till yellow colour persisted. After a few min, the excess of CH_2N_2 was destroyed with AcOH. Column purification using

neutral alumina (hexane-ethyl acetate, 9.5 : 0.5) afforded the keto ester 103b (765 mg, 70%) as a colourless liquid.

IR : 2950, 1780, 1730, 1210 cm^{-1}

^1H NMR : δ 6.50 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 6.28 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.58 (3H, s, -COOMe), 3.18-2.90 (2H, m, bridgehead CH; >CHCOOMe), 2.85 (1H, dd, $J_1 = J_2$ = 4 Hz), 2.10 (1H, ddd, J_1 = 12 Hz, J_2 = 10 Hz, J_3 = 4 Hz, exo-H_3), 1.58 (1H, dd, J_1 = 12 Hz, J_2 = 5 Hz, endo-H_3).

^{13}C NMR : δ 201.89, 172.83, 134.41, 130.12, 51.82, 48.47, 46.00, 37.65, 25.82.

Analysis : $C_9H_{10}O_3$: Calcd. : C, 65.05; H, 6.07
Found : C, 65.00; H, 6.01.

Methyl bicyclo[2.2.1]heptan-7-one-2-endo-carboxylate (104b):

A solution of unsaturated keto ester 103b (1 g, 6.0 mmol) in 4 ml of dry ethyl acetate was hydrogenated at atmospheric pressure over 5% Pd/C (5 mg) for a period of 20-30 min. The catalyst was filtered and the solvent removed to furnish the ester 104b (1 g, 100%).

IR : 2950, 1770, 1730, 1200 cm^{-1}

^1H NMR : δ 3.72 (3H, s, -COOMe), 3.02 (1H, m, >CHCOOMe), 2.30-1.50 (8H, series of m).

^{13}C NMR : δ 213.36, 173.48, 51.88, 41.17, 38.59, 38.41, 26.82, 23.41, 18.88.

Analysis : $C_9H_{12}O_3$: Calcd. : C, 64.27; H, 7.19
Found : C, 64.15; H. 7.16.

7,7-Dimethoxybicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (83):[46]

Liquid NH_3 (250 ml) was placed in a 500 ml two neck R.B. flask equipped with a condenser with KOH guard tube and acid 101 (5 g, 14.9 mmol) in dry THF (3-4 ml) was added to it. Freshly cut sodium metal pieces were added slowly till the blue colour persisted. Work-up as described earlier and crystallisation from hexane furnished 83 (2.2 g, 73%).

mp. : 84-85°C (Lit. 86°C)

Methyl 7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (105):[46b,c]

To a solution of 83 (2 g, 10.10 mmol) in dry ether (25 ml) was added an excess of ethereal solution of CH_2N_2 at 0°C till yellow colour persisted. After few minutes, the excess of CH_2N_2 was destroyed with AcOH. Evaporation of the solvent and column purification using silica gel (15% ethyl acetate-hexane) furnished ester 105 (1.82 g, 85%) as a colourless liquid.

7,7-Dimethoxy-5-endo-ethynylbicyclo[2.2.1]hept-2-ene (107):

Into a dry 250 ml two necked R.B. flask equipped with a septum dry N_2 inlet was introduced ester 105 (800 mg, 3.77 mmol) in dry dichloromethane (70 ml). After cooling the reaction vessel to -78°C, DIBAL-H (4 ml of 1.2 M solution in toluene, 4.80 mmol) was added and the reactants stirred for 45 min at -78°C. The reaction was quenched with MeOH and diluted with dichloromethane. The organic layer was washed

and dried. Removal of the solvent furnished the crude aldehyde 106.

To a suspension of bromomethyltriphenylphosphonium bromide (2.07 g, 4.75 mmol) in dry THF (25 ml) at -78°C was added freshly sublimed potassium t-butoxide (1.07 g, 9.54 mmol) in THF (10 ml) and the mixture stirred for 20 min at -78°C. To the yellow ylide formed was added the above aldehyde 106 in THF (5 ml) and the mixture stirred for 30 min at -78°C. The reaction mixture was warmed slowly to 0°C and stirred further for 30 min. THF was removed completely and water (20 ml) was added. It was then extracted with hexane (3 x 30 ml). The combined organic layer was washed with water and dried. Solvent was removed and the residue was charge on a silica gel column. Elution with 2% ethyl acetate-hexane furnished 107 (302 mg, 45%).

IR : 3050, 2950, 2110, 1120, 1080, 730 cm^{-1}

^1H NMR : δ 6.34-6.08 (2H, m, olefinic), 3.18 (3H, s, -OMe), 3.14 (4H, with a distinct s of -OMe), 2.98 (1H, br s), 2.82 (1H, m), 2.42-2.04 (1H, m, exo-H_6), 1.89 (1H, d, J = 2 Hz, -C≡CH), 1.04 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 135.06, 131.59, 118.30, 87.59, 67.53, 51.88, 49.59, 48.82, 44.76, 32.94, 26.29.

5-endo-Ethynylbicyclo[2.2.1]hept-2-ene-7-one (103c):

A mixture of ketal 107 (72 mg, 0.41 mmol) and amberlyst-15 (50 mg) in moist acetone (3 ml) was refluxed for 3 h. Amberlyst resin was filtered and the solvent was

removed. The residue was purified by column chromatography using silica gel (10 g, elution with 5% ethyl acetate-hexane) to furnish 103c (39 mg, 73%).

IR : 2950, 1780, 1100, 710 cm^{-1}

^1H NMR : δ 6.67 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 6.53 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.18-2.94 (2H, m), 2.89 (1H, dd, $J_1 = J_2$ = 4 Hz), 2.54-2.16 (1H, m, exo-H_6), 1.98 (1H, d, J = 2 Hz, -C≡C<u>H</u>), 1.30 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 202.72, 134.71, 131.30, 85.59, 68.71, 50.18, 46.00, 31.12, 24.23.

5-endo-Ethenylbicyclo[2.2.1]hept-2-ene-7-one (103d):

A solution of 103c (50 mg, 0.38 mmol) in 1 ml of dry ethyl acetate was hydrogenated at atmospheric pressure over Lindlar catalyst (3 mg) for a period of 20 min. The catalyst was filtered and the solvent removed to furnish 103d (31 mg, 60%).

IR : 3075, 2975, 1770, 910, 710 cm^{-1}

^1H NMR : δ 6.57 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 6.37 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 5.84-5.28 (1H, m, -C<u>H</u>=CH_2), 5.14-4.86 (2H, m, -CH=C<u>H_2</u>), 3.06-2.70 (3H, m), 2.22 (1H, ddd, J_1 = 12 Hz, J_2 = 10 Hz, J_3 = 4 Hz, exo-H_6), 1.07 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 204.83, 140.01, 133.89, 130.53, 115.53,

51.59, 46.70, 37.47, 29.35.

Oxime of bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde: 108:

To a solution of aldehyde 106 [prepared *via* DIBAL-H reduction of ester 105 (1.8 g, 8.49 mmol) as described above] in dry dichloromethane (20 ml) were added hydroxylamine hydrochloride (626 mg, 9.0 mmol) and pyridine (0.75 ml, 9.3 mmol) at room temperature. The reaction mixture was stirred for 30 min, diluted with dichloromethane and washed. The aqueous layer was extracted with dichloromethane. After the removal of the solvent, the residue was charged on a silica gel column. Elution with 30% ethyl acetate-hexane furnished a mixture of *cis* and *trans* oxime 108 (1 g, 60%).

IR : 3300, 3025, 2925, 1280, 1110, 1070 cm^{-1}

5-endo-Cyano-7,7-dimethoxybicyclo[2.2.1]hept-2-ene (109):

To a mixture of *cis*, *trans* oxime 108 (1 g, 5.08 mmol) in dry dichloromethane (10 ml) and pyridine (1 ml, 12.36 mmol) at 0°C was added p-toluenesulfonylchloride (1 g, 5.24 mmol). The reaction mixture was allowed to warm to room temperature slowly and stirred for 4-5 h. Water (10 ml) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed and dried. Removal of solvent and column purification using silica gel column (elution with 10% ethyl acetate hexane) furnished 109 (591 mg, 65%).

mp. : 63-64°C

IR : 3050, 2950, 2230, 1290, 1110, 1080 cm^{-1}

^{1}H NMR : δ 6.38 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 HZ, olefinic), 6.21 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.20-3.02 (8H, m with distinct singlets of -OMe at 3.18 and 3.14), 2.92 (1H, m, bridgehead CH), 2.30 (1H, ddd, J_1 = 12 Hz, J_2 = 8 Hz, J_3 = 4 Hz, exo-H_6), 1.27 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 137.06, 130.77, 122.48, 118.00, 52.35, 49.88, 47.59, 44.65, 30.47, 25.76.

Analysis : $C_{10}H_{13}NO_2$: Calcd.: C, 67.02; H, 7.31; N, 7.82
Found : C, 66.95; H, 7.25; N, 7.70.

5-endo-Cyanobicyclo[2.2.1]hept-2-ene-7-one (103a):

A mixture of 109 (400 mg, 2.24 mmol) and amberlyst-15 (50-100 mg) in moist acetone was refluxed for 18 h. Amberlyst resin was filtered and the solvent was removed. The residue was purified by passing it successively through neutral alumina (elution with 40% ethyl acetate hexane) and silica gel (elution with 25% ethyl acetate-hexane) columns to obtain 103a (178 mg, 60%).

mp. : low melting

IR : 2950, 2230, 1780, 1120, 1080 cm^{-1}

^{1}H NMR : δ 6.80 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 6.63 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 3.30-3.10 (2H, m, bridgehead CH; >CHCN), 3.02 (1H, m, bridgehead CH), 2.42 (1H, ddd, J_1 = 12 Hz, J_2 = 10 Hz, J_3 = 4 Hz, exo-H_6), 1.53 (1H, dd, J_1 = 12 Hz, J_2 =

4 Hz, endo-H_6).

^{13}C NMR : δ 199.87, 136.24, 130.83, 120.53, 47.76, 45.12, 28.29, 23.53.

Analysis : C_8H_7NO: Calcd. : C, 72.16; H, 5.29; N, 10.52
Found : C, 72.10; H, 5.26; N, 10.48.

2-endo-Cyanobicyclo[2.2.1]heptan-7-one (104a):

A solution of 103a (150 mg, 1.13 mmol) in 2 ml of dry ethyl acetate was hydrogenated at atmospheric pressure over 5% Pd/C (5 mg) for a period of 20 min. The catalyst was filtered and the solvent was removed to furnish the saturated ketone 104a (135 mg, 90%).

mp. : 80-90°C

IR : 2950, 2250, 1770, 1120 cm^{-1}

^1H NMR : δ 3.24-2.98 (1H, m, >CHCN), 2.52-1.52 (8H, series of m).

^{13}C NMR : δ 210.89, 120.53, 40.06, 37.47, 29.82, 24.53, 23.29, 19.35.

Analysis : C_8H_9NO: Calcd. : C, 71.09; H, 6.71; N, 10.36
Found : C, 71.00; H, 6.69; N, 10.30.

Methyl 7,7-dimethoxybicyclo[2.2.1]heptane-2-endo-carboxylate (111):

A solution of unsaturated ester 105 (2.4 g, 11.32 mmol) in 5 ml dry ethyl acetate was shaken in a Parr hydrogenation apparatus over 10% Pd/C (30 mg) at a pressure of 25 psi. After 30 min, the catalyst was filtered and the solvent was removed to furnish the saturated ester 111 (2.4 g, 100%)

IR : 2925, 1725, 1190, 1110, 1060 cm^{-1}

^{1}H NMR : δ 3.63 (3H, s, -COOMe), 3.23 (3H, s, -OMe), 3.21 (3H, s, -OMe), 3.14-2.86 (1H, m, >CH-COOMe), 2.31 (1H, m), 2.00 (1H, m), 1.92-1.64 (4H, m), 1.38-1.06 (2H, m).

^{13}C NMR : δ 175.59, 114.65, 51.65, 50.65, 50.47, 43.29, 41.29, 37.94, 29.70, 27.06, 22.64.

7,7-Dimethoxybicyclo[2.2.1]heptane-2-endo-carboxaldehyde (112):

Into a dry 250 ml two necked R.B. flask equipped with a septum, dry N_2 inlet was introduced ketal ester 111 (2.4 g, 11.22 mmol) in dry dichloromethane (120 ml). After cooling the reaction vessel to -78°C, DIBAL-H (13 ml of 1.2 M solution in toluene, 15.6 mmol) was added and the reactants stirred for 45 min. The reaction was quenched with MeOH and diluted with dichloromethane. The organic layer was washed and dried. Removal of solvent furnished the crude aldehyde 112.

7,7-Dimethoxy-2-endo-ethynylbicyclo[2.2.1]heptane (113):

To a suspension of chloromethyl triphenylphosphonium chloride (5.38 g, 15.5 mmol) in dry THF (80 ml) at -78°C was added freshly sublimed potassium t-butoxide (3.47 g, 31 mmol) in THF (15 ml) and the mixture stirred for 20 min at -78°C. To the yellow ylide formed was added the above aldehyde 112 in dry THF (5 ml) and the mixture stirred further for 1.5 h during which time it was allowed to warm to room temperature slowly. Work-up as described earlier

furnished a residue which was charged on a silica gel column. Elution with 1% ethyl acetate-hexane furnished haloalkene (1.21 g, 50%).

IR : 2950, 1320, 1190, 1110, 1070, 720 cm^{-1}

^1H NMR : δ 6.04-5.68 (2H, m, -CH=CHCl), 3.24 (3H, s, -OMe), 3.20 (3H, s, -OMe), 2.28-0.80 (9H, series of m).

To a solution of the above haloalkene (530 mg, 2.45 mmol) in dry THF (4 ml) under N_2 atmosphere at 0°C was added freshly sublimed potassium t-butoxide (825 mg, 7.36 mmol) in THF (3 ml). The reaction mixture was allowed to warm to room temperature and stirred overnight. Usual work-up and column purification using silica gel (20 g, elution with 1% ethyl acetate-hexane) furnished 113 (375 mg, 85%).

IR : 2950, 1340, 1200, 1120, 1080 cm^{-1}

^1H NMR : δ 3.22 (3H, s, -OMe), 3.20 (3H, s, -OMe), 3.00-2.72 (1H, m, >CH-C≡CH), 2.28-1.00 (9H, series of m).

^{13}C NMR : δ 114.12, 87.35, 69.29, 50.41, 42.00, 37.88, 35.88, 28.53, 27.35, 21.76.

2-endo-Ethynylbicyclo[2.2.1]heptan-7-one (104c):

A mixture of 113 (160 mg, 0.89 mmol) and amberlyst-15 (50 mg) in moist acetone (5 ml) was refluxed for 10-12 h. Amberlyst resin was filtered and the solvent was removed. The residue was purified by passing it successively through neutral alumina (elution with 30% ethyl acetate hexane) and silica gel (elution with 5% ethyl acetate hexane) columns to

furnish 104c (61 mg, 51%).

IR : 2950, 1770, 1120 cm^{-1}

^1H NMR : δ 3.14-2.80 (1H, m, >CH-C≡CH), 2.52-1.32 (9H, series of m).

^{13}C NMR : δ 214.53, 85.06, 70.77, 42.17, 38.76, 33.00, 25.23, 24.00, 18.35.

7,7-Dimethoxy-5-endo-hydroxymethylbicyclo[2.2.1]hept-2-ene (80):[46a]

To a suspension of $LiAlH_4$ (300 mg, 7.89 mmol) in dry ether (75 ml) was added mono ester 105 (1.1 g, 5.19 mmol) in ether (35 ml) and the mixture stirred for 4-5 h at room temperature. Excess of $LiAlH_4$ was destroyed by carefully adding few drops of ethyl acetate to the cooled reaction mixture. A saturated solution of Na_2SO_4 was added dropwise with stirring till a granular precipitate was formed. The precipitate was filtered and washed thoroughly with ethyl acetate. The filterate and the ethyl acetate washings were combined, washed and dried. Removal of solvent afforded the crude alcohol 80 (936 mg, 98%).

7,7-Dimethoxy-5-endo-methoxymethylbicyclo[2.2.1]hept-2-ene (134):

To a suspension of NaH (125 mg, 60%, 3.13 mmol) in dry THF (1 ml) under nitrogen atmosphere, a solution of 80 (480 mg, 2.61 mmol) in THF (2 ml) was added. The mixture was stirred for 20 min at room temperature during which time a white slurry was formed. To this slurry, MeI (445 mg, 3.13

mmol) in THF (1 ml) was added and stirring was continued for another 20 min. Usual work-up furnished a residue which was charged on a silica gel column. Elution with 20% ethyl acetate-hexane furnished 134 (470 mg, 91%) as colourless liquid.

IR : 3050, 2900, 1300, 1100 cm^{-1}

^1H NMR : δ 6.15 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 6.01 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.30 (3H, s, -OMe), 3.22 (3H, s, -OMe), 3.16 (3H, s, -OMe), 3.04 (2H, d, J = 8 Hz, $-CH_2OMe$), 2.93 (1H, m, bridgehead CH), 2.77 (1H, m, bridgehead CH), 2.56 (1H, m, $>CH-CH_2OMe$), 2.03 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, exo-H_6), 0.51 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 134.12, 131.00, 119.30, 75.18, 58.59, 51.76, 49.53, 46.53, 44.47, 35.82, 27.23.

2-endo-Methoxymethylbicyclo[2.2.1]heptan-7-one (132b):

A solution of 134 (400 mg, 2.02 mmol) in 2 ml of dry ethyl acetate was hydrogenated at atmospheric pressure over 5% Pd/C (5 mg) for a period of 20 min. The catalyst was filtered and the solvent was removed to furnish the saturated ether 132b (400 mg, 100%).

IR : 2950, 1190, 1110, 1075 cm^{-1}

^1H NMR : δ 3.30 (2H, d, J = 8 Hz, $-CH_2OMe$), 3.29 (3H, s, -OMe), 3.23 (3H, s, -OMe), 3.22 (3H, s, -OMe), 2.60-2.20 (1H, m, $>CH-CH_2OMe$), 2.12-1.00 (7H,

series of m), 0.80-0.58 (1H, m, endo-H_3).

^{13}C NMR : δ 114.88, 74.65, 58.76, 50.41, 50.23, 39.59, 37.70, 36.06, 31.94, 27.70, 20.29.

A mixture of the saturated ether obtained above (400 mg, 2 mmol) and amberlyst-15 (50 mg) in moist acetone (4 ml) was refluxed for 1.5 h. Amberlyst resin was filtered and the solvent was removed. The residue was charged on a silica gel column and eluted with 10% ethyl acetate-hexane to furnish 132b (222 mg, 72%).

IR : 2900, 1770, 1110 cm^{-1}

^1H NMR : δ 3.40 (2H, d, J = 8 Hz, $-CH_2OMe$), 3.28 (3H, s, $-OMe$), 2.36 (1H, m, $>CH-CH_2OMe$), 2.16-1.24 (7H, series of m), 0.94 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_3).

^{13}C NMR : δ 215.60, 73.29, 58.65, 40.53, 38.76, 32.12, 28.35, 24.53, 16.47.

$NaBH_4$ reduction of the anhydride 49: Formation of lactone 135:

To a solution of 49 (950 mg, 4.24 mmol) in dry THF (4 ml) at 0°C was added $NaBH_4$ (161 mg, 4.24 mmol) under N_2. The reaction mixture was stirred at 0-15°C for 1.5 h. Work-up as described earlier furnished a residue which was charged on a silica gel column. Elution with 50% ethyl acetate-hexane furnished 135 (735 mg, 83%).

IR : 2950, 1760, 1280, 1180, 1100, 1060, 1000 cm^{-1}

^1H NMR : δ 6.20 (2H, dd, $J_1 = J_2$ = 2 Hz, olefinic), 4.24 (1H, dd, $J_1 = J_2$ = 8 Hz), 3.74 (1H, dd, J_1 = 8

Hz, J_2 = 3 Hz), 3.28-2.94 (4H, series of m), 3.14 (3H, s, -OMe), 3.08 (3H, s, -OMe).

^{13}C NMR : δ 177.71, 133.94, 132.36, 121.18, 69.47, 52.06, 49.82, 48.29, 47.29, 45.12, 37.06.

Hydrolysis of the lactone 135: Formation of 136:

A mixture of 135 (700 mg, 3.33 mmol) and amberlyst-15 (25 mg) in moist acetone (5 ml) was refluxed for 10-12 h. Amberlyst resin was filtered and the solvent was removed. The residue was charged on a neutral alumina column and eluted with 50% ethyl acetate-hexane to furnish 136 (340 mg, 64%).

mp. : 155-156°C

IR : 2975, 1780, 1760, 1380, 1200, 1000 cm^{-1}

^{1}H NMR : δ 6.62 (2H, m, olefinic), 4.44 (1H, dd, J_1 = 10 Hz, J_2 = 8 Hz), 3.92 (1H, dd, J_1 = 10, J_2 = 3 Hz), 3.52-3.14 (4H, series of m).

^{13}C NMR : δ 198.18, 175.65, 132.95, 131.30, 70.41, 50.29, 47.76, 41.65, 34.06.

Analysis : $C_9H_8O_3$: Calcd. : C, 65.85; H, 4.91
Found : C, 65.78; H, 4.89.

Hydrogenation of the lactone 136: Formation of 133

A solution of 136 (300 mg, 1.83 mmol) in 3 ml of dry ethyl acetate was hydrogenated at atmospheric pressure over 5% Pd-C (5 mg) for a period of 30 min. The catalyst was filtered and the solvent was removed to furnish the saturated ketone 133 in near quantitative yield.

IR : 2950, 1770, 1740, 1380, 1180, 990 cm^{-1}

^1H NMR (200 MHz) : δ 4.53 (1H, d of 1/2 ABq, J_1 = 10 Hz, J_2 = 8 Hz, $-C\underline{H}_2OCO-$), 4.41 (1H, d of 1/2 ABq, J_1 = 10 Hz, J_2 = 3 Hz, $-C\underline{H}_2OCO-$), 3.25-3.03 (2H, m), 2.44 (1H, m, bridgehead C<u>H</u>), 2.18 (1H, dd, J_1 = J_2 = 4 Hz, bridgehead C<u>H</u>), 2.02-1.70 (4H, series of m).

^{13}C NMR : δ 209.89, 176.30, 68.18, 41.53, 40.00, 38.94, 33.53, 19.47, 16.00.

2-<u>exo</u>-Cyanobicyclo[2.2.1]heptan-7-one (<u>132a</u>):

Into a solution of 2-<u>exo</u>-cyano-7-isopropylidenenorbornane <u>137a</u> (300 mg, 1.86 mmol) in dry dichloromethane at -78°C was bubbled ozone until blue color appeared. Excess ozone was flushed out with a slow stream of nitrogen and DMSO (0.5 ml) was carefully added to the reaction mixture at -78°C. It was then allowed to warm-up to room temperature slowly and stirred for 30 min. The solvent was removed and the residue was charged on a silica gel column. Elution with 25% ethyl acetate-hexane furnished ketone <u>132a</u> (165 mg, 65%).

IR : 2925, 2250, 1770, 1130 cm^{-1}

^1H NMR : δ 2.76 (1H, dd, J_1 = 9 Hz, J_2 = 6 Hz, <u>endo</u>-$\underline{H}_2$), 2.28-1.40 (8H, series of m).

^{13}C NMR : δ 210.66, 120.83, 41.82, 36.88, 29.88, 25.94, 22.70(2C).

General procedure for diazomethane (DAM) ring expansion of 7-norbornanone derivatives:

To a solution of 7-norbornanone derivative (2 mmol) in 10 ml of dry ether containing 10% methanol was added an excess of ethereal solution of diazomethane at 0°C till yellow colour persisted. The reaction mixture was allowed to stand in the dark in a freezer at 0-5°C for 10-24 h during which time the reaction was monitored by tlc. Excess of diazomethane was destroyed with acetic acid when ca.80% (tlc) of starting ketone had been consumed.

DAM ring expansion of (47a):

The reaction was performed as described above. Column chromatography using neutral alumina and elution with 30% ethyl acetate hexane furnished 118a in 50% yield.

IR : 2950, 1720, 1430, 1350, 1200 cm^{-1}

^1H NMR : δ 3.68 (6H, s, -COOMe), 3.04 (2H, m), 2.68-2.48 (2H, m), 2.36-1.20 (6H, series of m).

^{13}C NMR : δ 213.42, 172.88, 171.83, 51.82, 44.35, 43.76, 43.23, 39.65, 30.59, 20.41, 18.41.

Analysis : $C_{12}H_{16}O_5$: Calcd. : C, 59.99; H, 6.71
Found : C, 60.14; H, 6.74.

DAM ring expansion of (47b):

The reaction was performed as described above. Column purification using neutral alumina and elution with 15% ethyl acetate hexane furnished 118b in 55% yield.

IR : 2900, 1720, 1200, 1110, 950 cm^{-1}

^1H NMR : δ 3.64-3.34 (4H, m, $-CH_2OMe$), 3.29 (3H, s,

-OMe), 3.26 (3H, s, -OMe), 2.34-1.24 (10H, series of m).

^{13}C NMR : δ 216.89, 71.41, 70.24, 58.65, 58.47, 45.12, 44.35, 37.23, 33.76, 30.00, 19.53, 17.53.

Analysis : $C_{12}H_{20}O_3$: Calcd. : C, 67.89; H, 9.50
Found : C, 67.75; H, 9.45.

DAM ring expansion of (47c):

The reaction was performed as described above. Column chromatography using neutral alumina and elution with 4% ethyl acetate hexane furnished 118c in 52% yield.

mp. : <40°C

IR : 3050, 2950, 1720, 990, 910 cm^{-1}

^1H NMR : δ 6.14-5.72 (2H, m, olefinic), 5.16-4.88 (4H, m, olefinic), 2.92-2.42 (2H, m, >CHCH=CH_2), 2.40-1.20 (8H, series of m).

^{13}C NMR : δ 216.60, 138.71, 136.59, 116.59, 116.06, 47.82, 45.12, 43.94, 40.65, 33.88, 19.88, 17.76.

Analysis : $C_{12}H_{16}O$: Calcd. : C, 81.77; H, 9.15
Found : C, 81.99; H, 9.20.

DAM ring expansion of (47e):

The reaction was performed as described above. Column chromatography using silica gel and elution with 2% ethyl acetate hexane furnished 118e in 58% yield.

IR : 2950, 1725, 1460, 1080 cm^{-1}

^1H NMR : δ 2.28-1.16 (14H, series of m), 0.87 (3H, t, J

= 7 Hz, $-CH_2C\underline{H}_3$), 0.83 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

^{13}C NMR : δ 218.95, 45.53, 45.23, 40.35, 37.12, 30.53, 20.82, 19.70, 19.17, 17.06, 13.11, 12.94.

Analysis : $C_{12}H_{20}O$: Calcd. : C, 79.94; H, 11.18
Found : C, 79.99; H, 11.19.

DAM Ring expansion of (104a):

The reaction was performed as described above. Filteration through neutral alumina (30% ethyl acetate-hexane) afforded a mixture of bicyclic ketones 119a and 120a (68%) in a ratio 71 : 29 which were separated by column chromatography using silica gel and elution with 20% ethyl acetate-hexane.

119a:

mp. : 174-175°C

IR : 2950, 2250, 1720, 1110 cm^{-1}

^1H NMR : δ 3.16-2.92 (1H, m), 2.50 (1H, m), 2.40-1.60 (9H, series of m).

^{13}C NMR : δ 212.18(s), 120.95(s), 43.70(d), 43.53(t), 29.82(t), 27.17(d), 24.61(d), 23.70(t), 19.29(t).

Analysis : $C_9H_{11}NO$: Calcd. : C, 72.45; H, 7.43; N, 9.39
Found : C, 72.28; H, 7.45; N, 9.36.

120a:

mp. : 167-168°C

IR : 2950, 2250, 1720, 1110 cm^{-1}

^{1}H NMR : δ 2.96-2.72 (1H, m), 2.56-1.60 (10H, series of m).

^{13}C NMR : δ 213.19, 122.24, 43.53, 41.06, 31.41, 27.94, 26.70, 22.35, 20.58.

Analysis : $C_9H_{11}NO$: Calcd. : C, 72.45; H, 7.43; N, 9.39
Found : C, 72.25; H, 7.40; N, 9.35.

DAM Ring expansion of (104b):

The reaction was performed as described above. Filtration through neutral alumina (20% ethyl acetate-hexane) afforded a mixture of bicyclic ketones 119b and 120b (64%) in a ratio of 63 : 37 (glc) which were separated by column chromatography using silica gel and elution with 10% ethyl acetate-hexane

119b:

mp. : 35-36°C

IR : 2950, 1730, 1200 cm^{-1}

^{1}H NMR : δ 3.71 (3H, s, -COOMe), 3.00-2.70 (1H, m), 2.60 (1H, m), 2.36-1.50 (9H, series of m).

^{13}C NMR : δ 214.95(s), 174.36(s), 52.18(q), 44.59(d), 43.82(t), 38.29(d), 27.70(d), 27.47(t), 24.29(t), 19.23(t).

Analysis : $C_{10}H_{14}O_3$: Calcd. : C, 65.91; H, 7.74
Found : C, 65.85; H, 7.72.

120b:

mp. : 64-65°C

IR : 2950, 1730, 1210 cm^{-1}

^{1}H NMR : δ 3.72 (3H, s, -COOMe), 2.84-1.40 (11H, series of m).

^{13}C NMR : δ 216.01(s), 175.12(s), 52.00(q), 44.47(t), 41.82(d), 41.17(d), 31.47(d), 25.35(t), 22.47(t), 20.64(t).

Analysis : $C_{10}H_{14}O_3$: Calcd. : C, 65.91; H, 7.74
Found : C, 65.79; H, 7.69.

DAM Ring expansion of (132a):

The reaction was performed as described above. Filteration through neutral alumina (elution with 40% ethyl acetate-hexane) afforded a mixture of bicyclic ketones 138a and 139a (66%) in a ratio of 61 : 39. The regioisomeric ketones 138a and 139a were separated by converting them into ethylene ketal as follows:

Ketalisation of mixture of 138a and 139a:

In an R.B. flask fitted with a Dean-Stark water separator was placed regioisomeric mixture of ketones 138a and 139a (150 mg, 1 mmol), ethylene glycol (0.17 ml, 3 mmol), PPTS (5-10 mg) and benzene. The contents of the flask were refluxed for 1 h with stirring. The reaction mixture was cooled and quenched by adding saturated $NaHCO_3$ solution (2 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extract was washed and dried. Removal of solvent furnished a regioisomeric mixture of ketals which were separated by column chromatography using neutral alumina. Elution with 8% ethyl acetate-hexane first furnished ethylene ketal of 139a and on further elution pure

ethylene ketal of 138a was obtained.

Ethylene ketal of 139a:

mp. : 67-68°C

IR : 2950, 2250, 1130, 1020 cm^{-1}

^1H NMR : δ 4.06-3.72 (4H, m, $-OCH_2CH_2O-$), 2.76-2.48 (1H, m), 2.32-1.20 (10H, series of m).

Ethylene ketal of 138a:

mp. : 83-84°C

IR : 2950, 2250, 1130, 1080 cm^{-1}

^1H NMR : δ 4.16-3.78 (4H, m, $-OCH_2CH_2O-$), 2.82-2.54 (1H, m), 2.08-1.16 (10H, series of m).

Hydrolysis of ethylene ketal of (139a):

A mixture of ketal of 139a (32 mg, 0.22 mmol) and amberlyst-15 (25 mg) in moist acetone (4 ml) was stirred at room temperature for 2 h. Amberlyst resin was filtered and the solvent was removed. Filteration through a small silica gel column (elution with 40% ethyl acetate hexane) furnished the bicyclic ketone 139a in quantitative yield.

139a:

mp. : 147-148°C

IR : 2950, 2250, 1720, 1110 cm^{-1}

^1H NMR (200 MHz) : δ 2.93 (1H, m, >CHCN), 2.73 (1H, dd of 1/2 ABq, J_1 = 19 Hz, $J_2 = J_3$ = 2 Hz), 2.51 (1H, m), 2.41-2.23 (3H, series of m), 2.13-2.00 (1H, m), 1.94-1.60 (4H, series of m).

^{13}C NMR : δ 213.12, 122.06, 40.88(2C), 31.53, 27.82,

26.17, 24.06, 22.00.

Analysis : $C_9H_{11}NO$: Calcd. : C, 72.45; H, 7.43; N, 9.39
Found : C, 72.38; H, 7.45; N, 9.33.

Hydrolysis of ethylene ketal of (138a):

The reaction was performed as described for ketal of 139a to furnish the bicyclic ketone 138a in quantitative yield.

138a:

mp. : 157-158°C

IR : 2950, 2250, 1720, 1110 cm^{-1}

^1H NMR (200 MHz) : δ 3.05 (1H, ddd, J_1 = 11 Hz, J_2 = 5.2 Hz, J_3 = 2.8 Hz, >CHCN), 2.57 (1H, m), 2.46-2.13 (4H, series of m), 2.03-1.82 (3H, series of m), 1.80-1.62 (2H, series of m).

^{13}C NMR : δ 211.24(s), 121.36(s), 44.59(d), 44.17(t), 30.12(t), 27.11(d), 25.70(d), 23.06(t), 22.47(t).

Analysis : $C_9H_{11}NO$: Calcd. : C, 72.45; H, 7.43; N, 9.39
Found : C, 72.38; H, 7.45; N, 9.33.

DAM Ring expansion of (132b):

The reaction was performed as described above. Filtration through neutral alumina (20% ethyl acetate-hexane) afforded a mixture of bicyclic ketones 138b and 139b (72%) in a ratio of 60 : 40 which were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

138b:

IR : 2950, 1720, 1110 cm^{-1}

^1H NMR : δ 3.30 (2H, d, J = 8 Hz), 3.24 (3H, s, -OMe), 2.30-1.40 (10H, series of m), 1.24-0.96 (1H, m).

^{13}C NMR : δ 216.77, 74.12, 58.47, 43.70, 43.47, 31.94, 28.82, 27.70, 24.82, 17.41.

Analysis : $C_{10}H_{16}O_2$: Calcd. : C, 71.39; H, 9.59
Found : C, 71.25; H, 9.55.

139b:

IR : 2950, 1720, 1110 cm^{-1}

^1H NMR : δ 3.32-3.20 (5H, m with a distinct s of -OMe at 3.28), 2.24-1.10 (11H, series of m).

^{13}C NMR : δ 217.59, 75.41, 58.76, 45.41, 42.35, 35.35, 28.94, 27.29, 23.23, 19.11.

Analysis : $C_{10}H_{16}O_2$: Calcd. : C, 71.39; H, 9.59
Found : C, 71.25; H, 9.55.

DAM Ring expansion of (133):

The reaction was performed as described above. Filteration through neutral alumina (elution with ethyl acetate) afforded a mixture of bicyclic ketones 121 and 122 (55%) in a ratio of 63 : 37. The regioisomeric mixture of ketones were separated by converting them into ethylene ketal as follows:

Ketalisation of mixture of 121 and 122:

The reaction was performed as described above for 138a

and 139a. The mixture of ketals were separated by column chromatography using neutral alumina. Elution with 20% ethyl acetate hexane furnished ethylene ketal of 121 and on further elution pure ethylene ketal of 122 was obtained.

Ethylene ketal of 121:

mp. : 128-129°C

IR : 2900, 1750, 1180, 1110, 1010 cm^{-1}

^1H NMR : δ 4.40 (1H, dd, J_1 = 8 Hz, J_2 = 10 Hz, $-C\underline{H}_2-OCO-$), 4.10 (1H, dd, J_1 = 3 Hz, J_2 = 10 Hz, $-C\underline{H}_2OCO-$), 3.90 (4H, m, $-OC\underline{H}_2C\underline{H}_2O-$), 2.98 (1H, m), 2.76-1.30 (9H, series of m).

^{13}C NMR : δ 179.59, 109.71, 70.71, 64.18, 64.06, 40.29, 38.29, 35.64, 33.59, 30.00, 18.17, 16.88.

Ethylene ketal of 122:

mp. : 112-113°C

IR : 2900, 1750, 1180, 1110, 1010 cm^{-1}

^1H NMR : δ 4.44 (1H, dd, J_1 = J_2 = 10 Hz, $-C\underline{H}_2OCO-$), 4.18 (1H, dd, J_1 = 4 Hz, J_2 = 10 Hz, $-C\underline{H}_2OCO-$), 3.92 (4H, m, $-OC\underline{H}_2C\underline{H}_2O-$), 3.18-2.84 (1H, m), 2.84-2.52 (1H, m), 2.36-2.00 (1H, m), 2.00-1.40 (7H, series of m).

^{13}C NMR : δ 179.30, 109.30, 69.82, 64.18, 64.06, 41.12, 40.88, 35.94, 32.17, 28.64, 20.29, 15.06.

Hydrolysis of ethylene ketal of 121:

A mixture ethylene ketal of 121 (64 mg, 0.29 mmol) and amberlyst-15 (25 mg) in moist acetone (4 ml) was refluxed for 2 h. Amberlyst was filtered off. Removal of solvent

and filteration through a small silica gel column (elution with 25% ethyl acetate hexane) furnished the ketone 121 in quantitative yield.

121:

mp. : 190-191°C

IR : 2925, 1760, 1720, 1170, 1000 cm^{-1}

^1H NMR : δ 4.46 (1H, dd, $J_1 = J_2 = 8$ Hz, $-C\underline{H}_2OCO-$), 4.20 (1H, dd, $J_1 = 4$ Hz, $J_2 = 10$ Hz, $-C\underline{H}_2OCO-$), 2.84 (2H, m), 2.60 (1H, m), 2.28 (1H, br s), 2.16 (2H, m), 1.80 (2H, 1/2 ABq, J = 12 Hz), 1.64 (2H, 1/2 ABq, J = 12 Hz).

^{13}C NMR : δ 212.54, 177.12, 70.29, 43.35, 42.59, 38.41, 36.35, 31.29, 18.76, 17.94.

Analysis : $C_{10}H_{12}O_3$: Calcd. : C, 66.65; H, 6.71
Found : C, 66.58; H, 6.77.

Hydrolysis of ethylene ketal of 122:

The reaction was performed as described above for ethylene ketal of 121 to furnish the ketone 122 in quantitative yield.

122:

mp. : 203-204°C

IR : 2925, 1760, 1720, 1170 cm^{-1}

^1H NMR : δ 4.60-4.16 (2H, m, $-CH_2OCO-$), 2.90 (2H, m), 2.6 (1H, m), 2.40-2.08 (3H, m), 2.00-1.60 (4H, m).

^{13}C NMR : δ 213.01, 177.95, 68.41, 44.76, 43.47, 41.17, 33.00, 30.29, 20.94, 16.70.

Analysis : $C_{10}H_{12}O_3$: Calcd. : C, 66.65; H, 6.71
Found : C, 66.58; H, 6.77.

General procedure for $NaBH_4$ reduction of ketones:

A solution of ketone (0.2 mmol) in dry methanol (3 ml) was cooled in an ice-bath and sodium borohydride (0.2 mmol) was added to it. The reaction mixture stirred for 15-30 min till the starting ketone was fully consumed. Reactions were continuously monitored by tlc. Methanol was removed at room temperature under reduced pressure and the residue diluted with water (5 ml). The aqueous layer was extracted with ethyl acetate (3 x 10 ml) and the combined organic layer washed and dried. Removal of solvent gave the mixture of syn- and anti-alcohols in quantitative yield. The product ratios were determinated by ^1H NMR analyses of the crude reaction mixture.

General procedure for $LiAlH_4$ reduction of ketones:

To a suspension of $LiAlH_4$ (0.1 mmol) in dry ether (5 ml) cooled in an ice-bath, the ketone (0.2 mmol) in ether (2 ml) was added under N_2. The reaction mixture was stirred for 15-20 min till the starting ketone was fully consumed. Reactions were continuously monitored by tlc. After the usual work-up, drying, and evaporation of solvent, the crude mixture was analysed using ^1H NMR spectroscopy.

In case of the diester 47a, the $LiAlH_4$ reduction was carried out at lower temperature (-23°C).

General procedure for $(t\text{-BuO})_3LiAlH$ reduction:

Same as described above for $LiAlH_4$ reduction.

General procedure for DIBAL-H reduction:

To a solution of ketone (0.2 mmol) in dry dichloromethane cooled to -78°C, DIBAL-H (0.2 ml of 1.2 M solution in toluene, 0.24 mmol) was added under N_2 and the reaction mixture was stirred for 15 min. The reaction was quenched with MeOH and diluted with dichloromethane, washed and dried. Removal of solvent furnished a mixture of syn and anti alcohols (90-95%). The product ratios were determined by the ^1H NMR analyses of the crude reaction mixture.

General procedure for methyllithium addition:

To a solution of ketone (0.2 mmol) in dry ether cooled in an ice bath, methyllithium (0.3 ml of 1.4 M solution in ether) was added under N_2 and the reaction mixture was stirred for 15-30 min. The mixture was diluted with ether, washed and dried. Removal of solvent furnished mixture of syn and anti tertiary alcohols (85-95%). The product ratios were determined by the ^1H NMR analysis of the crude reaction mixture.

$NaBH_4$ Reduction of (47a):

The reaction was performed as described in the general procedure to furnish 65a : 66a (16 : 84) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

$LiAlH_4$ Reduction of (47a):

The reaction was performed at -23°C and as described in the general procedure to furnish 65a : 66a (13 : 87) in nearly quantitative yield.

$(t\text{-}BuO)_3LiAlH$ Reduction of (47a):

The reaction was performed at 0°C and as described in the general procedure to furnish 65a : 66a (23 : 77) in nearly quantitative yield.

65a:

IR : 3400, 2950, 1720, 1190 cm^{-1}

^1H NMR (Fig.2) : δ 4.20 (1H, br s, >CHOH), 3.66 (6H, s, -COOMe), 3.46 (2H, br s, >CHCOOMe), 2.31 (2H, br s, bridgehead CH), 1.90-1.36 (4H, series of m, $H_{5,6}$).

^{13}C NMR : δ 173.71, 79.65, 51.47, 44.35, 43.70, 21.35.

HRMS : $C_{11}H_{16}O_5$:Calcd.: 228.0997 (M^+), 197.0813 (M^+-OCH_3)
Found : 197.0815

66a:

IR : 3400, 2950, 1720, 1190 cm^{-1}

^1H NMR (Fig.3) : δ 4.02 (1H, br s, >CHOH), 3.64 (6H, s, -COOMe), 2.98 (2H, br s, >CHCOOMe), 2.34 (2H, br s, bridgehead CH), 1.80 (4H, br s, $H_{5,6}$).

^{13}C NMR : δ 172.54, 78.35, 51.47, 44.00, 43.47, 20.94.

HRMS : $C_{11}H_{16}O_5$: Calcd. : 228.0998
Found : 228.1018.

Methyllithium addition to (47a):

The reaction was performed as described in the general procedure to furnish 47a : 48a (traces : >90) in 90% yield.

47a:

mp. : 95-96°C

IR : 3450, 2950, 1730, 1200 cm^{-1}

^1H NMR (Fig.4) : δ 3.64 (6H, s, -COOMe), 3.57 (2H, br s, >CHCOOMe), 2.00 (2H, br s, bridgehead CH), 1.92-1.50 (4H, series of m), 1.45 (3H, s, >CMeOH).

^{13}C NMR : δ 173.83, 83.77, 51.41, 47.59, 45.00, 21.82, 21.06.

HRMS : $C_{12}H_{18}O_5$: Calcd. : 242.1154,
210.0892 ($M^+ - CH_3OH$)
Found : 210.0890.

48a:

IR : 3450, 2950, 1730, 1200 cm^{-1}

^1H NMR (Fig.5) : δ 3.64 (6H, s, -COOMe), 3.10 (2H, br s, >CHCOOMe), 2.02 (2H, br s, bridgehead CH), 1.85 (4H, br s), 1.45 (3H, s, >CMeOH).

^{13}C NMR : δ 172.77, 82.83, 51.53, 47.41, 44.29, 22.53, 20.35.

HRMS : $C_{12}H_{18}O_5$: Calcd. : 242.1154,
210.0892 ($M^+ - CH_3OH$)
Found : 210.0895.

$NaBH_4$ Reduction of (47b):

The reaction was performed as described in the general

procedure to furnish 65b : 66b (60 : 40) in nearly quantitative yield. The isomers could not be separated by column chromatography but the access to the individual isomers 65b and 66b was possible through hydrogenation of the corresponding 7-norbornenols 95b and 96b respectively which were obtained by $NaBH_4$ reduction of norbornenone 91b.

65b:

mp. : 58-56°C

IR : 3400, 2900, 1100 cm^{-1}

^1H NMR (500 MHz) : δ 4.13 (1H, s, >CHOH), 3.55-3.30 (4H, series of m, $-CH_2OMe$), 3.33 (6H, s, -OMe), 2.66 (2H, br s, $>CHCH_2OMe$), 2.07 (2H, br s, bridgehead CH), 1.42 (4H, s, $H_{5,6}$).

^{13}C NMR : δ 79.35, 70.47, 58.65, 43.47, 36.29, 19.70.

HRMS : $C_{11}H_{20}O_3$: Calcd.: 200.1412
Found : 200.1421.

66b:

IR : 3400, 2900, 1100 cm^{-1}

^1H NMR (500 MHz) : δ 4.11 (1H, s, >CHOH), 3.55-3.30 (4H, series of m, $-CH_2OMe$), 3.31 (6H, s, -OMe), 2.25 (2H, br s, $>CHCH_2OMe$), 2.11 (2H, br s, bridgehead CH), 1.71 (2H, 1/2 ABq, J = 8 Hz, exo-$H_{5,6}$), 1.48 (2H, 1/2 ABq, J = 8 Hz, endo-$H_{5,6}$).

^{13}C NMR : δ 79.35, 70.00, 58.65, 43.88, 37.06, 19.47.

HRMS : $C_{11}H_{20}O_3$: Calcd. : 200.1412
Found : 200.1421.

Methyllithium addition to (47b):

The reaction was performed as described in the general procedure to furnish 67b : 68b (66 : 34) in 90% yield. The two isomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

67b:

mp. : 81-82°C

IR : 3425, 2950, 1200, 1100 cm^{-1}

^1H NMR (Fig.6) : δ 3.54-3.34 (4H, m, $-CH_2OMe$), 3.32 (6H, s, $-OMe$), 2.76 (2H, m, $>CH-CH_2OMe$), 1.74 (2H, br s, bridgehead CH), 1.48 (4H, br s), 1.41 (3H, s, $>CMeOH$).

^{13}C NMR : δ 83.18, 70.77, 58.71, 46.88, 37.82, 21.29, 20.23.

HRMS : $C_{12}H_{22}O_3$: Calcd. : 214.1568,
182.1307 ($M^+ - CH_3OH$)
Found : 182.1300.

68b:

IR : 3425, 2950, 1200, 1100 cm^{-1}

^1H NMR (Fig.7) : δ 3.48-3.32 (4H, m, $-CH_2OMe$), 3.31 (6H, s, $-OMe$), 2.35 (2H, br s, $>CHCH_2OMe$), 1.76 (6H, m), 1.46 (3H, s, $>CMeOH$).

^{13}C NMR : δ 83.12, 70.65, 58.82, 47.23, 37.65, 20.94, 20.29.

$NaBH_4$ Reduction of (47c):

The reaction was performed as described in the general procedure to furnish 65c : 66c (64 : 36) in quantitative yield. The isomers were separated by column chromatography

using silica gel and elution with 4% ethyl acetate-hexane.

$LiAlH_4$ Reduction of (47c):

The reaction was performed as described in the general procedure to furnish 65c : 66c (66 : 34) in nearly quantitative yield.

65c:

IR : 3200, 2950, 1630, 1070, 910 cm^{-1}

^1H NMR (Fig.9) : δ 6.12-5.74 (2H, m, $-C\underline{H}=CH_2$), 5.14-4.90 (4H, m, $-CH=CH_2$), 4.18 (1H, s, $>C\underline{H}OH$), 3.08 (2H, m, $>C\underline{H}-CH=CH_2$), 2.02 (2H, m, bridgehead C$\underline{H}$), 1.62 (2H, 1/2 ABq, J = 10 Hz, exo-$\underline{H}_{5,6}$), 1.44 (2H, 1/2 ABq, J = 10 Hz, endo-$\underline{H}_{5,6}$).

^{13}C NMR : δ 137.94, 116.47, 80.59, 46.88, 43.88, 20.35.

HRMS : $C_{11}H_{16}O$: Calcd. : 164.1201
Found : 164.1210.

66c:

IR : 3200, 2950, 1630, 1070, 910 cm^{-1}

^1H NMR (Fig.10) : δ 6.04-5.66 (2H, m, $-C\underline{H}=CH_2$), 5.12-4.80 (4H, m, $-C\underline{H}=CH_2$), 4.14 (1H, s, $>C\underline{H}OH$), 2.68 (2H, m, $>C\underline{H}-CH=CH_2$), 2.08 (2H, br s, bridgehead C$\underline{H}$), 1.72 (4H, br s, $\underline{H}_{5,6}$).

^{13}C NMR : δ 136.24, 115.24, 74.59, 45.94, 43.29, 18.76.

Methyllithium addition to (47c):

The reaction was performed as described in the general procedure to furnish 67c : 68c (73 : 27) in 90% yield. The two isomers were separated by column chromatography using

silica gel and elution with 5% ethyl acetate-hexane.

67c:

IR : 3350, 3060, 2950, 1625, 910 cm^{-1}

^1H NMR : δ 6.14-5.70 (2H, m, olefinic), 5.16-4.84 (4H, m, olefinic), 3.22 (2H, m, >C<u>H</u>-CH=CH_2), 1.84-1.48 (6H, m), 1.44 (3H, s, >C<u>Me</u>OH).

^{13}C NMR : δ 138.48, 116.36, 84.24, 50.23, 45.41, 21.35, 20.88

Mass (m/e) : 178 (M^+, 1), 160(35), 145(30), 135(52), 98(100), 91(70), 79(94) (from E:Z mixture).

68c:

IR : 3340, 3060, 2950, 1625, 910 cm^{-1}

^1H NMR : δ 6.14-5.70 (2H, m, olefinic), 5.16-4.84 (4H, m, olefinic), 2.82 (2H, m, >C<u>H</u>-CH=CH_2), 1.84-1.48 (6H, m), 1.52 (3H, s, >C<u>Me</u>OH).

^{13}C NMR : δ 138.06, 116.58, 83.47, 50.41, 44.94, 21.47.

$NaBH_4$ Reduction of (47d):

The reaction was performed as described in the general procedure to furnish 65d : 66d (75 : 25) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 2% ethyl acetate-hexane.

65d:

IR : 3300, 3050, 2950, 1070, 905 cm^{-1}

^1H NMR (300 MHz) (Fig.12) : δ 6.04-5.92 (1H, m, -C<u>H</u>=CH_2), 5.09-5.03 (2H, m, -CH=C<u>H</u>$_2$), 4.15 (1H, s, >C<u>H</u>OH), 2.97 (1H, m, >C<u>H</u>-CH=CH_2), 2.24 (1H, m, >C<u>H</u>-CH_2CH_3), 2.00

(1H, s, bridgehead C<u>H</u>), 1.93 (1H, s, bridgehead C<u>H</u>), 1.68-1.20 (6H, series of m), 0.83 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

HRMS : $C_{11}H_{18}O$: Calcd. : 166.1358
Found : 166.1356.

<u>66d</u>:

IR : 3300, 3050, 2950, 1070, 905 cm^{-1}

^1H NMR (300 MHz) (Fig.13) : δ 5.97-5.83 (1H, m, $-C\underline{H}=CH_2$), 5.08-4.93 (2H, m, $-CH=C\underline{H}_2$), 4.11 (1H, s, >C<u>H</u>OH), 2.57 (1H, m, >C<u>H</u>CH=CH_2), 2.04 (1H, s, bridgehead C<u>H</u>), 1.98 (1H, s, bridgehead C<u>H</u>), 1.86 (1H, m, >C<u>H</u>-CH_2CH_3), 1.66-1.20 (6H, series of m), 0.78 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

$NaBH_4$ Reduction of (<u>47e</u>):

The reaction was performed as described in the general procedure to furnish <u>65e</u> : <u>66e</u> (80 : 20) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 0.5% ethyl acetate-benzene.

$LiAlH_4$ Reduction of (<u>47e</u>):

The reaction was performed as described in the general procedure to furnish <u>65e</u> : <u>66e</u> (79 : 21) in nearly quantitative yield.

$(t\text{-BuO})_3LiAlH$ Reduction of (<u>47e</u>):

The reaction was performed as described in the general procedure to furnish <u>65e</u> : <u>66e</u> (71 : 29) in nearly quanti-

tative yield.

65e:

IR : 3300, 2950, 1070 cm^{-1}

^1H NMR (Fig.14) : δ 4.10 (1H, s, >C<u>H</u>OH), 2.12 (2H, m, >C<u>H</u>CH_2CH_3), 1.96 (2H, br s, bridgehead C<u>H</u>), 1.68-1.20 (8H, series of m), 0.81 (6H, t, J = 7 Hz, -CH_2C<u>H</u>$_3$).

^{13}C NMR : δ 76.65, 43.47, 38.88, 19.11, 18.64, 13.35.

HRMS : $C_{11}H_{20}O$: Calcd. : 168.1514
Found : 168.1514.

66e:

IR : 3300, 2950, 1070 cm^{-1}

^1H NMR (Fig.15) : δ 4.06 (1H, s, >C<u>H</u>OH), 2.00 (2H, br s, bridgehead C<u>H</u>), 1.80 (2H, m, >C<u>H</u>CH_2CH_3), 1.64-1.20 (8H, series of m), 0.78 (6H, t, J = 7 Hz, -CH_2C<u>H</u>$_3$).

^{13}C NMR : δ 80.18, 44.29, 40.12, 18.70, 18.53, 13.17.

HRMS : $C_{11}H_{20}O$: Calcd. : 168.1514
Found : 168.1509.

Methyllithium addition to (<u>47e</u>):

The reaction was performed as described in the general procedure to furnish <u>67e</u> : <u>68e</u> (83 : 17) in 90% yield.

<u>67e</u>:

IR : 3400, 2975, 1160, 1100 cm^{-1}

^1H NMR (300 MHz) : δ 2.35-2.21 (2H, m, >C<u>H</u>CH_2CH_3), 1.73-1.21 (13H, series of m with a distinct singlet of >C<u>Me</u>OH at 1.42), 0.79 (6H, t, J = 7 Hz, -CH_2C<u>H</u>$_3$).

^{13}C NMR : δ 83.12, 46.82, 40.53, 21.70, 19.47, 18.94,

13.29.

HRMS : $C_{12}H_{22}O$: Calcd. : 182.1671

Found : 182.1667.

68e:

IR : 3400, 2975, 1160, 1100 cm^{-1}

^1H NMR (300 MHz) : δ 1.97-1.87 (2H, m, >C<u>H</u>CH_2CH_3), 1.77-1.23 (13H series of m with a distinct singlet of >C<u>Me</u>OH of 1.46), 0.77 (6H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

^{13}C NMR : δ 83.23, 47.35, 40.23, 20.41, 20.11, 19.06, 13.23.

HRMS : $C_{12}H_{22}O$: Calcd. : 182.1671,

164.1565 (M^+-H_2O

Found : 164.1577.

$NaBH_4$ Reduction of (77a):

The reaction was performed as described in the general procedure to furnish 84a : 85a (<15 : >85) in quantitative yield. The isomers were separated by column chromatography using silica gel and elution with 1% ethyl acetate-hexane.

84a:

IR : 3425, 2950, 1110, 890 cm^{-1}

^1H NMR (Fig.16) : δ 4.49 (1H, s, >C<u>H</u>OH), 4.36 (2H, br s, >C<u>H</u>-O-), 4.04 (2H, 1/2 ABq, J = 9 Hz, $-C\underline{H}_2$-O-), 3.70 (2H, 1/2 ABq, J = 9 Hz, $-C\underline{H}_2$O-), 2.52 (4H, br s).

^{13}C NMR : δ 78.12, 72.06, 69.00, 50.12, 39.29.

85a:

mp. : 235°C (sublim.)

IR : 3425, 2950, 1110, 890 cm^{-1}

^1H NMR (200 MHz) (Fig.17) : δ 4.17 (1H, s, >C<u>H</u>OH), 4.11 (2H, 1/2 ABq, J = 9 Hz, -C<u>H</u>$_2$O-), 3.99 (2H, dd, $J_1 = J_2 = 2.2$ Hz, >C<u>H</u>-O-), 3.78 (2H, dd of 1/2 ABq, $J_1 = 9$ Hz, $J_2 = J_3 = 1.8$ Hz, -C<u>H</u>$_2$O-), 2.83 (2H, br s), 2.56 (2H, m).

^{13}C NMR : δ 77.06, 69.24, 68.47, 51.23, 39.53.

Analysis : $C_9H_{12}O_3$: Calcd. : C, 64.27; H, 7.19
Found : C, 64.30; H, 7.23.

$NaBH_4$ Reduction of (<u>77b</u>):

The reaction was performed as described in the general procedure to furnish <u>84b</u> : <u>85b</u> (36 : 64) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 10% ethyl acetate-chloroform.

<u>84b</u>:

IR : 3350, 2925, 1080, 990, 890 cm^{-1}

^1H NMR (Fig.18) : δ 4.58 (1H, dd, $J_1 = 7$ Hz, $J_2 = 5$ Hz, >C<u>H</u>-O-), 4.26 (1H, br s, >C<u>H</u>OH), 3.79 (1H, d of 1/2 ABq, $J_1 = 8$ Hz, $J_2 = 4$ Hz, -C<u>H</u>$_2$O-), 3.61 (1H, 1/2 ABq, $J_1 = 8$ Hz, -C<u>H</u>$_2$O-), 2.54-1.76 (5H, series of m), 1.34-1.00 (2H, m).

^{13}C NMR : δ 80.53, 80.00, 75.00, 51.23, 38.70, 36.47, 36.17, 35.59.

<u>85b</u>:

mp. : 187-188°C

IR : 3250, 2925, 1080, 990, 890 cm^{-1}

^{1}H NMR (Fig.19) : δ 4.22 (1H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C<u>H</u>-O-), 4.01 (1H, s, >C<u>H</u>OH), 3.76 (2H, m, -C<u>H</u>$_2$O-), 2.76-2.04 (3H, series of m), 1.92 (1H, br s), 1.80-1.48 (1H, m), 1.32-1.06 (2H, m).

^{13}C NMR : δ 79.18, 77.30, 74.18, 51.70, 38.94, 38.06, 37.41, 34.47.

$NaBH_4$ Reduction of (<u>77c</u>):

The reaction was performed as described in the general procedure to furnish <u>84c</u> : <u>85c</u> (31 : 69) in quantitative yield. The isomers were separated by column chromatography using silica gel and elution with 60% ethyl acetate-hexane.

<u>84c</u>:

IR : 3400, 2950, 1760, 1190, 1090, 980 cm^{-1}

^{1}H NMR (200 MHz) : δ 5.02 (1H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C<u>H</u>OCO-), 4.36 (1H, br s, >C<u>H</u>OH), 3.11-3.02 (1H, m), 2.63-2.28 (2H, series of m), 2.13-1.97 (1H, m), 1.95-1.55 (3H, series of m).

^{13}C NMR : δ 180.92, 81.48, 79.62, 50.51, 40.86, 37.32, 34.15, 30.83.

<u>85c</u>:

IR : 3400, 2950, 1760, 1190, 1090, 980 cm^{-1}

^{1}H NMR (200 MHz) : δ 4.73 (1H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C<u>H</u>OCO-), 4.26 (1H, br s, >C<u>H</u>OH), 3.12 (1H, m), 2.80 (1H, dd, J_1 =11 Hz, J_2 = 5 Hz), 2.59-2.43 (1H, m), 2.31 (1H, m), 1.95-1.55 (3H, series of m).

^{13}C NMR : δ 181.33, 78.44, 78.26, 51.27, 41.34, 38.40, 35.33, 31.27.

$NaBH_4$ Reduction of (91a):

The reaction was performed as described in the general procedure to furnish 95a : 96a (45 : 55) in quantitative yield. The two diastereomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

95a:

IR : 3450, 3060, 2950, 1730, 1340, 1200 1080 cm^{-1}

^1H NMR (Fig.21) : δ 6.14 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.68 (1H, s, >CHOH), 3.62 (6H, s, -COOMe), 3.56 (2H, br s, >CHCOOMe), 2.92 (2H, m, bridgehead CH).

^{13}C NMR : δ 173.48, 133.53, 82.35, 51.65, 50.18, 45.53.

Analysis : $C_{11}H_{14}O_5$: Calcd. : C, 58.40; H, 6.24
Found : C, 58.36; H, 6.26.

96a:

IR : 3450, 3060, 2950, 1740, 1200, 1040 cm^{-1}

^1H NMR (Fig.22) : δ 6.28 (2H, br s, olefinic), 3.84 (1H, br s, >CHOH), 3.60 (6H, s, -COOMe), 3.28 (2H, br s, >CHCOOMe), 3.16 (2H, br s, bridgehead CH).

^{13}C NMR : δ 172.01, 132.18, 85.71, 51.76, 51.65, 45.47.

Methyllithium addition to (91a):

The reaction was performed as described in the general procedure to furnish 97a : 98a (10 : 90) in 90% yield. The two isomers were separated by column chromatography using silica gel and elution with 20% ethyl acetate-hexane.

97a:

IR : 3450, 3060, 2950, 1720, 1200 cm^{-1}

^1H NMR (Fig.23) : δ 6.18 (2H, dd, $J_1 = J_2$ = 2 Hz, olefinic), 3.74 (2H, br s, >CHCOOMe), 3.59 (6H, s, -COOMe), 2.72 (2H, br s, bridgehead CH), 1.34 (3H, s, >CMeOH).

^{13}C NMR : δ 173.53, 134.71, 89.88, 54.59, 51.53, 46.94, 20.41.

98a:

IR : 3475, 3060, 2950, 1730, 1200 cm^{-1}

^1H NMR (Fig.24) : δ 6.34 (2H, dd, $J_1 = J_2$ = 2 Hz, olefinic), 3.61 (6H, s, -COOMe), 3.42 (2H, m, >CHCOOMe), 2.90 (2H, m, bridgehead CH), 1.32 (3H, s, >CMeOH).

^{13}C NMR : δ 172.24, 134.30, 89.88, 55.00, 51.70, 46.06, 18.70.

$NaBH_4$ Reduction of (91b):

The reaction was performed as described in the general procedure to furnish 95b : 96b (88 : 12) in quantitative yield. The two diastereomers were separated by column chromatography using silica gel and elution with 35% ethyl acetate-hexane.

95b:

IR : 3450, 3050, 2900, 1090 cm^{-1}

^1H NMR : δ 6.03 (2H, dd, $J_1 = J_2$ = 2 Hz, olefinic), 3.64 (1H, br s, >CHOH), 3.32 (6H, s, -OMe), 3.38-3.00 (4H, m, $-CH_2OMe$), 2.72 (4H, br s).

^{13}C NMR : δ 134.12, 82.88, 71.94, 58.71, 49.70, 38.17.

Analysis : $C_{11}H_{18}O_3$: Calcd. : C, 66.64; H, 9.15
Found : C, 66.45; H, 9.12.

96b:

IR : 3400, 3050, 2900, 1090 cm^{-1}

^1H NMR : δ 6.16 (2H, br s, olefinic), 3.90 (1H, br s, >CHOH), 3.28 (6H, s, -OMe), 3.20-2.96 (4H, m, $-CH_2OMe$), 2.95 (2H, br s), 2.51 (2H, m, >CH-CH_2OMe).

Methyllithium addition to (91b):

The reaction was performed as described in the general procedure to furnish 97b : 98b (74 : 26) in 85% yield. The two isomers were separated by column chromatography using silica gel and elution with ethyl acetate.

97b:

IR : 3425, 3050, 2950, 1090, 720 cm^{-1}

^1H NMR : δ 6.04 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 3.28 (6H, s, -OMe), 3.28-2.80 (6H, series of m), 2.52 (2H, br s, bridgehead CH), 1.30 (3H, s, >CMeOH).

^{13}C NMR : δ 135.06, 90.06, 72.18, 58.59, 54.12, 39.70, 20.94.

98b:

IR : 3450, 3050, 2925, 1100 cm^{-1}

^1H NMR : δ 6.22 (2H, br s, olefinic), 3.28 (6H, s, -OMe), 3.18-2.88 (4H, m, $-CH_2OMe$), 2.80-2.48 (4H, m, $>CHCH_2OMe$, bridgehead CH), 1.32 (3H, s, >CMeOH).

^{13}C NMR : δ 134.83, 90.83, 71.94, 58.76, 55.18, 39.35, 18.64.

$NaBH_4$ Reduction of (91c):

The reaction was performed as described in the general procedure to furnish 95c : 96c (87 : 13) in quantitative yield. Only the major diastereomer could be obtained by column chromatography using silica gel and elution with 25% ethyl acetate-hexane.

95c:

IR : 3400, 3050, 2900, 1090 cm^{-1}

^1H NMR : δ 6.04 (2H, dd, $J_1 = J_2 = 2$ Hz, olefinic), 4.00-3.72 (4H, m, $-C\underline{H}_2OAc$), 3.66 (1H, br s, $>C\underline{H}OH$), 2.71 (4H, br s), 2.04 (6H, $-OCO\underline{Me}$).

^{13}C NMR : δ 171.30, 134.18, 82.71, 63.76, 49.76, 37.70, 21.00.

$NaBH_4$ Reduction of (103a):

The reaction was performed as described in the general procedure to furnish 114a : 115a (44 : 56) in quantitative yield. The two diastereomers were separated by column chromatography using silica gel and elution with 40% ethyl acetate-hexane.

114a:

mp. : 89-90°C

IR : 3400, 3050, 2250, 1300, 1100, 710 cm^{-1}

^1H NMR (Fig.25) : δ 6.24 (1H, dd of 1/2 ABq, $J_1 = 6$ Hz, $J_2 = 4$ Hz, $J_3 = 1$Hz, olefinic), 6.08 (1H, dd of 1/2 ABq, $J_1 = 6$ Hz, $J_2 = 4$ Hz, $J_3 = 1$Hz, olefinic), 3.72 (1H, br s, $>C\underline{H}OH$), 3.12 (1H, ddd, $J_1 = 9$ Hz, $J_2 = J_3 = 4$ Hz, $>C\underline{H}CN$), 2.93 (1H, m,

bridgehead C<u>H</u>), 2.70 (1H, bridgehead C<u>H</u>), 2.38 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.35 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$).

^{13}C NMR : δ 137.83, 131.89, 123.42, 82.41, 49.70, 46.35, 29.53, 24.88.

Analysis : C_8H_9NO : Calcd. : C, 71.09; H, 6.71; N, 10.36
Found : C, 71.15; H, 6.69; N, 10.25.

<u>115a</u>:

mp. : 44-45°C

IR : 3300, 2250, 1100, 740 cm^{-1}

^{1}H NMR (Fig.26) : δ 6.38 (1H, d of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, olefinic), 6.22 (1H, d of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, olefinic), 3.76 (1H, br s, >C<u>H</u>OH), 3.14 (1H, m, bridgehead C<u>H</u>), 3.02-2.80 (2H, m, >C<u>H</u>CN, bridgehead C<u>H</u>), 2.20 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.30 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$).

^{13}C NMR : δ 136.01, 129.94, 121.89, 86.06, 50.47, 47.53, 29.70, 24.76.

Analysis : C_8H_9NO : Calcd. : C, 71.09; H, 6.71; N, 10.36
Found : C, 71.21; H, 6.60; N, 10.32.

$NaBH_4$ Reduction of (<u>103b</u>):

The reaction was performed as described in the general procedure to furnish <u>114b</u> : <u>115b</u> (68 : 32) in quantitative yield. The two diastereomers were separated by column chromatography using silica gel and elution with 20% ethyl

acetate-hexane.

114b:

IR : 3400, 3050, 2925, 1700, 1200, 1070 cm^{-1}

^1H NMR (Fig.27) : δ 6.11 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 5.85 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 4 Hz, olefinic), 3.66 (1H, br s, >C<u>H</u>OH), 3.64 (3H, s, -COO<u>Me</u>), 3.20 (1H, ddd, J_1 = 9 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>COOMe), 2.91 (1H, m, bridgehead C<u>H</u>), 2.60 (1H, m, bridgehead C<u>H</u>), 2.14 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-$\underline{H}_6$), 1.48 (1H, dd, J_1 = 12 Hz, J_2 = 4Hz, <u>endo</u>-$\underline{H}_6$).

^{13}C NMR : δ 176.12, 136.53, 131.59, 83.47, 51.65, 49.59, 46.29, 40.70, 25.94.

115b:

IR : 3350, 3050, 2950, 1710, 1200, 1090 cm^{-1}

^1H NMR (Fig.28) : δ 6.21 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 5.96 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 3.84 (1H, s, >C<u>H</u>OH), 3.63 (3H, s, -COO<u>Me</u>), 3.16 (1H, br s, bridgehead C<u>H</u>), 3.06-2.76 (2H, m, >C<u>H</u>COOMe, bridgehead C<u>H</u>), 1.97 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-$\underline{H}_6$), 1.40 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-$\underline{H}_6$).

^{13}C NMR : δ 174.36, 134.71, 129.71, 86.94, 51.76, 50.88, 48.23, 40.06, 26.82.

$NaBH_4$ Reduction of (103c):

The reaction was performed as described in the general procedure to furnish 114c : 115c (72 : 28) in quantitative yield. The two diastereomers were separated by column chromatography using silica gel and elution with 2% ethyl acetate-hexane.

114c:

IR : 3300, 3050, 2950, 2125, 1070 cm^{-1}

^1H NMR (Fig.29) : δ 6.18 (1H, dd of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, J_3 = 1 Hz, olefinic), 6.04 (1H, dd of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, J_3 = 1 Hz, olefinic), 3.70 (1H, br s, >C<u>H</u>OH), 3.18-2.92 (1H, m, >C<u>H</u>-C≡CH), 2.78 (1H, m, bridgehead C<u>H</u>), 2.60 (1H, bridgehead C<u>H</u>), 2.31 (1H, ddd, J_1 = 11 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.90 (1H, d, J = 3 Hz, -C≡C<u>H</u>), 1.16 (1H, dd, J_1 = 11 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$).

^{13}C NMR : δ 136.24, 132.83, 88.35, 83.12, 67.24, 50.94, 46.53, 31.70, 25.59.

115c:

IR : 3300, 3050, 2950, 2125, 1070 cm^{-1}

^1H NMR (Fig.30) : δ 6.30 (1H, d of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, olefinic), 6.16 (1H, d of 1/2 ABq, J_1 = 5 Hz, J_2 = 3 Hz, olefinic), 3.74 (1H, br s, >C<u>H</u>OH), 3.00 (1H, br s, bridgehead C<u>H</u>), 2.94-2.72 (2H, m, >C<u>H</u>-C≡CH), bridgehead C<u>H</u>), 2.15 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$). 1.90 (1H, d, J = 3 Hz, -C≡C<u>H</u>), 1.04 (1H, dd, J_1 = 12

Hz, J_2 = 4 Hz, endo-H_6).

$NaBH_4$ Reduction of (103d):

The reaction was performed as described in the general procedure to furnish 114d : 115d (>90 : traces) in quantitative yield.

114d:

IR : 3300, 3050, 2925, 1070, 910 cm^{-1}

^1H NMR : δ 6.20-6.00 (1H, m, -CH=CH-), 6.00-5.84 (1H, m, -CH=CH-), 5.84-5.38 (1H, m, -CH=CH_2), 5.14-4.80 (2H, m, -CH=CH_2), 3.68 (1H, br s, >CHOH), 3.12-2.80 (1H, m, >CHCH=CH_2, 2.68-2.48 (2H, m, bridgehead CH), 2.14 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, exo-H_6), 0.96 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, endo-H_6).

^{13}C NMR : δ 142.42, 135.59, 132.48, 113.94, 83.88, 51.76, 46.65, 39.82, 29.29.

$NaBH_4$ Reduction of (104a):

The reaction was performed as described in the general procedure to furnish 116a : 117a (18 : 82) in 90% yield (based on starting material recovery). The two isomers could not be separated by column chromatography but the access to the individual isomers was possible through hydrogenation of the corresponding norbornenols 114a and 115a, respectively, which were obtained by $NaBH_4$ reduction of norbornenone 103a.

116a:

mp. : low melting

IR : 3250, 2950, 2240, 1090 cm^{-1}

^1H NMR (Fig.32) : δ 4.17 (1H, br s, >CHOH), 3.30-3.02 (1H, m, >CHCN), 2.52-1.16 (8H, series of m).

^{13}C NMR : δ 123.24, 79.30, 43.94, 40.65, 32.70, 27.76, 26.29, 22.17.

Analysis : $C_8H_{11}NO$: Calcd. : C, 70.04; H, 8.08; N, 10.21
Found : C, 69.95; H, 8.00; N, 10.18.

117a:

mp. : 72-73°C

IR : 3250, 2950, 2240, 1090 cm^{-1}

^1H NMR (Fig.33) : δ 3.96 (1H, br s, >CHOH), 2.88-2.60 (1H, m, >CHCN), 2.34-1.68 (6H, series of m), 1.56-1.26 (2H, m).

^{13}C NMR : δ 122.06, 78.41, 43.35, 40.00, 32.29, 27.17, 26.11, 22 .06.

Analysis : $C_8H_{11}NO$: Calcd. : C, 70.04; H, 8.08; N, 10.21
Found : C, 69.93; H, 8.11; N, 10.24.

$NaBH_4$ Reduction of (104b):

The reaction was performed as described in the general procedure to furnish 116b : 117b (32 : 68) in quantitative yield. The two isomers could not be separated by column chromatography but the access to the individual isomers was possible through hydrogenation of the corresponding norbornenols 114b and 115b, respectively, which were obtained by $NaBH_4$ reduction of norbornenone 103b.

116b:

IR : 3400, 2950, 1720, 1190, 1070 cm^{-1}

^1H NMR : δ 4.09 (1H, br s, >C<u>H</u>OH), 3.67 (3H, s, -COO<u>Me</u>), 3.33-3.05 (1H, m, >C<u>H</u>COOMe), 2.62 (1H, br s), 2.28 (1H, br s), 2.07-1.15 (6H, series of m).

^{13}C NMR : δ 176.48, 80.71, 51.59, 44.47, 43.17, 40.82, 28.88, 26.23, 22.06.

117b:

IR : 3350, 2950, 1720, 1190, 1040 cm^{-1}

^1H NMR : δ 4.02 (1H, br s, >C<u>H</u>OH), 3.67 (3H, s, -COO<u>Me</u>), 2.88-2.60 (1H, m, >C<u>H</u>COOMe), 2.32 (1H, m), 2.01 (1H, br s), 1.93-1.58 (4H, series of m), 1.44-1.16 (2H, m).

^{13}C NMR : δ 175.07, 79.70, 51.70, 44.17, 42.36, 40.76, 29.00, 26.17, 21.88.

$NaBH_4$ Reduction of (<u>104c</u>):

The reaction was performed as described in the general procedure to furnish <u>116c</u> : <u>117c</u> (31 : 69) in 95% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 10% ethyl acetate-hexane.

<u>116c</u>:

IR : 3250, 2925, 1160, 1080 cm^{-1}

^1H NMR (Fig.34) : δ 4.14 (1H, s, >C<u>H</u>OH), 3.24-2.98 (1H, m, >C<u>H</u>C≡CH), 2.46-1.16 (9H, series of m).

<u>117c</u>:

IR : 3250, 2925, 1160, 1080 cm^{-1}

^1H NMR (Fig.35) : δ 3.96 (1H, s, >C<u>H</u>OH), 2.73-2.60 (1H, >C<u>H</u>-C≡CH), 2.15-1.72 (5H, series of m), 1.55-1.12 (4H, series of m).

^{13}C NMR : δ 87.06, 79.35, 69.06, 45.12, 40.88, 35.23, 28.06, 26.59, 21.06.

$NaBH_4$ Reduction of (<u>118a</u>):

The reaction was performed as described in the general procedure to furnish <u>123a</u> : <u>124a</u> (30 : 70) in quantitative yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 20% ethyl acetate-hexane.

$(i\text{-}Bu)_2AlH$ Reduction of (<u>118a</u>):

The reaction was performed as described in the general procedure to furnish <u>123a</u> : <u>124a</u> (33 : 67) in 90% yield.

<u>123a</u>:

IR : 3450, 2950, 1730, 1440, 1200 cm^{-1}

^1H NMR (Fig.36) : δ 4.04 (1H, ddd, J_1 = 8 Hz, $J_2 = J_3$ = 4 Hz, >C<u>H</u>OH), 3.65 (6H, s, -COO<u>Me</u>), 3.29 (1H, 1/2 ABq, J = 10 Hz, >C<u>H</u>COO<u>Me</u>), 2.99 (1H, 1/2 ABq, J = 10 Hz, >C<u>H</u>COOMe), 2.20-1.00 (8H, series of m).

^{13}C NMR : δ 174.71, 174.13, 68.29, 51.53(2C), 43.66, 36.88(2C), 34.35, 27.92, 20.11, 19.06.

Analysis : $C_{12}H_{18}O_5$: Calcd. : C, 59.49; H, 7.49
Found : C, 60.05, H, 6.74.

<u>124a</u>:

IR : 3450, 2950, 1730, 1200 cm^{-1}

^{1}H NMR (Fig.37) : δ 4.00 (1H, ddd, J_1 = 8 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>OH), 3.66 (3H, s, -COO<u>Me</u>), 3.65 (3H, s, -COO<u>Me</u>), 2.80 (2H, br s, >C<u>H</u>COOMe), 2.20-1.20 (8H, series of m).

^{13}C NMR : δ 173.95, 173.53, 68.65, 51.65, 42.88, 41.94, 36.94, 34.12, 27.64, 20.94, 14.23.

$NaBH_4$ Reduction of (<u>118b</u>):

The reaction was performed as described in the general procedure to furnish <u>123b</u> : <u>124b</u> (48 : 52) in quantitative yield. The diastereomeric mixture of alcohols <u>123b</u> and <u>124b</u> were separated by converting them into corresponding acetates followed by column separation and hydrolysis.

Acetylation of mixture of <u>123b</u> and <u>124b</u>:

To a solution of <u>123b</u> and <u>124b</u> (0.2 mmol) in dry dichloromethane at 0°C was added DMAP (0.22 mmol) followed by acetic anhydride (0.22 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The mixture was then diluted with dichloromethane, washed and dried. Removal of solvent furnished a mixture of acetates (quantitative yield) which were separated by column chromatography using neutral alumina. Elution with 10% ethyl acetate-hexane first furnished <u>syn</u>-acetate derived from <u>123b</u> and on further elution pure <u>anti</u>-acetate derived from <u>124b</u> was obtained.

<u>syn</u>-acetate (derived from <u>123b</u>):

IR : 2875, 1720, 1240, 1100, 1010 cm^{-1}

^{1}H NMR : δ 4.90 (1H, ddd, J_1 = 10 Hz, J_2 = J_3 =4 Hz, >C<u>H</u>OAc), 3.74-3.38 (4H, m, >C<u>H$_2$</u>OMe), 3.33 (3H, s, -O<u>Me</u>), 3.32 (3H, s, -O<u>Me</u>), 2.66-1.06 (13H, series of m with a distinct singlet of -OCO<u>Me</u> at 2.02).

<u>anti</u>-acetate (derived from <u>124b</u>):

IR : 2875, 1720, 1240, 1100, 1010 cm^{-1}

^{1}H NMR : δ 4.88 (1H, ddd, J_1 = 10 Hz, J_2 = J_3 =4 Hz, >C<u>H</u>OAc), 3.72-3.24 (4H, m, -C<u>H$_2$</u>OMe), 3.32 (6H, s, -O<u>Me</u>), 2.26-1.20 (13H, series of m with a distinct singlet of -OCO<u>Me</u> at 2.03).

Hydrolysis of <u>syn</u>-acetate: (derived from <u>123b</u>):

A mixture of <u>syn</u>-acetate and 1.5% methanolic KOH solution (1 ml) was stirred at room temperature for 20 min. Methanol was removed under vacuum and water (2 ml) was added to the mixture. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic extract was washed and dried. Removal of solvent and filteration through a small silica gel column (elution with 50% ethyl acetate-hexane) furnished the bicyclic alcohol <u>123b</u> in 90% yield.

<u>123b</u>:

IR : 3400, 2900, 1110, 960 cm^{-1}

^{1}H NMR : δ 3.98 (1H, ddd, J_1 = 8 Hz, J_2 = J_3 =4 Hz, >C<u>H</u>OH), 3.68-3.24 (4H, m, -C<u>H$_2$</u>OMe), 3.32 (6H, s, -O<u>Me</u>), 2.68-2.32 (1H, m, >C<u>H</u>CH$_2$OMe), 2.32-1.10 (9H, series of m).

^{13}C NMR : δ 72.12, 71.82, 69.41, 58.53(2C), 38.00, 37.29, 34.41, 30.06, 27.11, 19.23, 18.94.

Hydrolysis of anti-acetate: (derived from 124b):

The reaction was performed as described above for syn-acetate to furnish the bicyclic alcohol 124b in 90% yield.

124b:

IR : 3400, 2900, 1110, 960 cm^{-1}

^{1}H NMR : δ 3.96 (1H, ddd, J_1 = 8 Hz, J_2 = J_3 = 4 Hz, >CHOH), 3.66-3.22 (4H, m, $-CH_2OMe$), 3.32 (3H, s, -OMe), 3.30 (3H, s, -OMe), 2.20-1.20 (10H, series of m).

^{13}C NMR : δ 72.20, 71.53, 70.12, 58.71(2C), 37.88, 36.70, 35.70, 34.41, 27.29, 20.47, 13.88.

$NaBH_4$ Reduction of (118c):

The reaction was performed as described in the general procedure to furnish 123c : 124c (50 : 50) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 8% ethyl acetate-hexane.

$(i\text{-}Bu)_2AlH$ Reduction of (118c):

The reaction was performed as described in the general procedure to furnish 123c : 124c (50 : 50) in 90% yield.

123c:

IR : 3350, 3050, 2925, 1020, 990, 910 cm^{-1}

^{1}H NMR (500 MHz) : δ 5.99-5.88 (2H, m, $-CH=CH_2$), 5.00-4.94 (4H, m, $-CH=CH_2$), 4.04 (1H, ddd, J_1 = 10 Hz, J_2 = J_3 =

4 Hz, >C<u>H</u>OH), 2.93 (1H, dd, $J_1 = J_2 =$ 10 Hz, >C<u>H</u>-CH=CH_2), 2.58 (1H, dd, $J_1 = J_2$ 10 Hz, >C<u>H</u>-CH=CH_2), 2.09 (1H, ddd, J_1 = 14 Hz, J_2 = 9 Hz, J_3 =4 Hz), 1.82 (1H, m), 1.73-1.19 (6H, series of m).

^{13}C NMR : δ 140.48, 139.89, 114.83, 114.65, 69.53, 44.59, 38.12, 37.82, 36.76, 31.23, 19.47, 19.00.

Analysis : $C_{12}H_{18}O$: Calcd. : C, 80.85; H, 10.18
Found : C, 80.80; H, 10.21.

<u>124c</u>:

IR : 3350, 3050, 2925, 1020, 990, 910 cm^{-1}

^1H NMR (500 MHz) : δ 5.99-5.88 (2H, m, -C<u>H</u>=CH_2), 5.02-4.93 (4H, m, -CH=C<u>H</u>$_2$), 4.04 (1H, m, >C<u>H</u>OH), 2.45 (1H, dd, $J_1 = J_2$ = 10 Hz, >C<u>H</u>-CH=CH_2), 2.38 (1H, dd, $J_1 = J_2$ = 10 Hz, >C<u>H</u>-CH=CH_2), 2.09 (1H, m), 1.85-1.25 (7H, series of m).

^{13}C NMR : δ 140.30, 139.54, 115.06, 114.95, 70.00, 43.59, 42.70, 38.06, 31.06, 20.53, 14.11.

Methyllithium addition to (<u>118c</u>):

The reaction was performed as described in the general procedure to furnish <u>123c</u>, R_1=Me : <u>124c</u>, R_1=Me (46 : 54) in 92% yield. The two isomers were separated by column chromatography using silica gel and elution with 8% ethyl acetate-hexane.

<u>123c</u>, **R_1=Me:**

IR : 3375, 3075, 2950, 1120, 1000, 910 cm^{-1}

^{1}H NMR (Fig.38) : δ 6.16-5.72 (2H, m, -C<u>H</u>=CH_2), 5.08-4.82 (4H, m, -CH=C<u>H</u>$_2$), 3.10 (1H, dd, $J_1 = J_2 = 10$ Hz, >C<u>H</u>-CH=CH_2), 2.58 (1H, dd, $J_1 = J_2 = 10$ Hz, >C<u>H</u>-CH=H_2), 1.84-1.10 (11H, series of m with a distinct singlet of -<u>Me</u> at 1.38).

^{13}C NMR : δ 140.66, 140.23, 114.84, 114.77, 71.82, 44.41, 43.39, 42.29, 38.35, 32.50, 30.22, 19.32, 17.73.

Analysis : $C_{13}H_{20}O$: Calcd. : C, 81.20; H, 10.48
Found : C, 81.10; H, 10.81.

<u>124c</u>, R_1=Me:

IR : 3375, 3075, 2950, 1120, 1000, 910 cm^{-1}

^{1}H NMR (Fig.39) : δ 6.15-5.72 (2H, m, -C<u>H</u>=CH_2), 5.08-4.80 (4H, m, -CH=C<u>H</u>$_2$), 2.59 (1H, dd, $J_1 = J_2 = 10$ Hz, >C<u>H</u>-CH=CH_2), 2.46 (1H, dd, $J_1 = J_2 =$ 10Hz, >C<u>H</u>-CH=CH_2), 1.86-1.12 (11H, series of m with a distinct singlet of -<u>Me</u> at 1.38).

^{13}C NMR : δ 140.46, 139.98, 115.00, 114.88, 71.91, 44.45, 43.78, 42.65, 41.05, 32.53, 30.00, 19.57, 15.58.

$NaBH_4$ Reduction of (<u>118e</u>):

The reaction was performed as described in the general procedure to furnish <u>123e</u> : <u>124e</u> (61 : 39) in quantitative yield.

(i-Bu)$_2$AlH Reduction of (<u>118e</u>):

The reaction was performed as described in the general procedure to furnish <u>123e</u> : <u>124e</u> (65 : 35) in 90% yield.

The pure isomers 123e and 124e were obtained by hydrogenating the corresponding divinyl derivatives 123c and 124c, respectively.

Hydrogenation of 123c:

A solution of divinyl alcohol 123c (15 mg, 0.08 mmol) in dry ethyl acetate (2 ml) was shaken in Parr hydrogenation apparatus over PtO_2 (2 mg) at a hydrogen pressure of 40 psi. After 20 min, the catalyst was filtered and the solvent was removed to furnish diethyl alcohol 123e (15 mg, 100%).

123e:

IR : 3350, 2925, 1460, 1030 cm^{-1}

^1H NMR : δ 3.97 (1H, ddd, J_1 = 10 Hz, $J_2 = J_3$ =4 Hz, >C<u>H</u>OH), 2.24-1.80 (2H, m), 1.80-1.06 (12H series of m), 0.85 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$), 0.82 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

^{13}C NMR : δ 70.24, 40.59, 38.70, 35.53(2C), 33.00, 27.64, 20.94, 20.47, 18.82(2C), 13.29.

Analysis : $C_{12}H_{122}O$: Calcd. : C, 79.06; H, 12.16
Found : C, 79.45; H, 12.29.

Hydrogenation of 124c:

The reaction was performed as described above for 123c to furnish diethyl alcohol 124e in quantitative yield.

124e:

IR : 3350, 2925, 1460, 1030 cm^{-1}

^1H NMR : δ 3.94 (1H, ddd, J_1 = 10 Hz, $J_2 = J_3$ =4 Hz, >C<u>H</u>OH), 2.40-1.82 (2H, m), 1.82-1.06 (12H,

series of m), 0.85 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$), 0.82 (3H, J = 7 Hz, $-CH_2C\underline{H}_3$).

^{13}C NMR : δ 71.06, 39.76, 38.65, 38.47, 35.06, 27.82, 21.00, 20.41, 20.06, 13.58, 13.47, 13.35.

Methyllithium addition to (118e):

The reaction was performed as described in the general procedure to furnish 123e, R_1=Me : 124e, R_1=Me (66 : 34) in 85% yield. The individual isomers 123e, R_1=Me and 124e, R_1=Me were obtained by hydrogenating the corresponding divinyl alcohols 123c, R_1=Me and 124c, R_1=Me respectively as described above for 123c, R_1=H.

123e, R_1=Me:

IR : 3350, 2950, 1460, 1110 cm^{-1}

^1H NMR (300 MHz) : δ 2.12 (1H, m), 1.70-1.07 (16H, series of m with a distinct singlet of $-\underline{Me}$ at 1.34), 0.86 (3H, J = 7 Hz, $-CH_2C\underline{H}_3$), 0.84 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$).

^{13}C NMR : δ 77.22, 44.92, 40.03, 39.49, 34.17, 30.27, 28.98, 20.89, 20.50, 18.63, 17.14, 13.32 (2C).

124e, R_1=Me:

IR : 3350, 2950, 1460, 1110 cm^{-1}

^1H NMR (300 MHz) : δ 1.82-1.19 (17H, series of m with a distinct singlet of $-\underline{Me}$ at 1.32), 0.86 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$), 0.83 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$).

^{13}C NMR : δ 72.57, 44.92, 39.92, 39.64, 37.03, 30.03, 28.82, 20.97, 20.66, 18.98, 14.96, 13.39, 13.28.

$NaBH_4$ Reduction of (119b):

The reaction was performed as described in the general procedure to furnish syn : anti (35 : 65) alcohols in quantitative yield.

$(i\text{-}Bu)_2AlH$ Reduction of (119b):

The reaction was performed as described in the general procedure to furnish syn : anti (34 : 65) alcohols in 95% yield.

syn-alcohol:

IR : 3400, 2950, 1730, 1200 cm^{-1}

^1H NMR (500 MHz) : δ 4.05-4.00 (1H, m, >CHOH), 3.69 (3H, S, -COOMe), 3.04 (1H, m, >CHCOOMe), 2.07-1.22 (10H, series of m) (from syn : anti mix).

^{13}C NMR : δ 176.06, 68.71, 51.59, 36.53, 36.29, 35.41, 27.94, 23.94, 19.70 (from syn : anti mix).

Analysis : $C_{10}H_{16}O_3$: Calcd. : C, 65.19; H, 8.75
Found : C, 65.25; H, 8.72.

anti-alcohol:

IR : 3350, 2950, 1730, 1200 cm^{-1}

^1H NMR (500 MHz) : δ 4.05-4.00 (1H, m, >CHOH), 3.70 (3H, s, -COOMe), 2.51 (1H, m, >CH-COOMe), 2.07-1.22 (10H, series of m) (from syn : anti mix).

^{13}C NMR : δ 177.30, 69.12, 51.76, 40.12, 34.64, 26.32, 24.32, 24.53, 14.76 (from syn : anti mix).

$NaBH_4$ Reduction of (120b):

The reaction was performed as described in the general procedure to furnish syn : anti (38 : 62) alcohols in

quantitative yield.

$(i\text{-Bu})_2AlH$ Reduction of (120b):

The reaction was performed as described in the general procedure to furnish syn : anti (39 : 61) alcohols in 95% yield.

syn-alcohol:

IR : 3300, 2950, 1730, 1190 cm^{-1}

^1H NMR (500 MHz) : δ 3.97 (1H, m, >CHOH), 3.68 (3H, S, -COOMe), 2.67 (1H, m, >CHCOOMe), 2.13-1.18 (10H, series of m) (from syn : anti mix).

^{13}C NMR : δ 176.48, 68.35, 51.65, 41.17, 37.76, 31.23, 28.00, 22.70, 21.00, 20.29 (from syn : anti mix).

Analysis : $C_{10}H_{16}O_3$: Calcd. : C, 65.19; H, 8.75
Found : C, 65.25; H, 8.71.

anti-alcohol:

IR : 3300, 2950, 1730, 1190 cm^{-1}

^1H NMR (500 MHz) : δ 3.97 (1H, m, >CHOH), 3.68 (3H, s, -COOMe), 2.45 (1H, m, >CHCOOMe), 2.13-1.18 (10H, series of m) (from syn : anti mix).

^{13}C NMR : δ 176.36, 68.71, 51.65, 40.65, 37.35, 31.64, 28.35, 25.88, 21.47, 17.76 (from syn : anti mix).

$NaBH_4$ Reduction of (121):

The reaction was performed as described in the general procedure to furnish syn : anti (34 : 66) alcohols in quan-

titative yield. The two isomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

syn-alcohol:

mp. : 161-162°C

IR : 3450, 2900, 1745, 1200, 1030 cm^{-1}

^1H NMR : δ 4.44 (1H, dd, $J_1 = J_2 = 10$ Hz, $-C\underline{H}_2OCO-$), 4.14 (1H, dd, $J_1 = J_2 = 10$ Hz, $-C\underline{H}_2OCO-$), 3.94 (1H, m, $>C\underline{H}OH$), 3.06 (1H, dd, $J_1 = 12$ Hz, $J_2 = 4$ Hz, $>C\underline{H}COO-$), 2.72 (1H, m, $>C\underline{H}CH_2O-$), 2.34-1.14 (8H, series of m).

Analysis : $C_{10}H_{14}O_3$: Calcd. : C, 65.91; H, 7.74
Found : C, 66.10; H, 7.78.

anti-alcohol:

mp. : 168-169°C

IR : 3450, 2900, 1750, 1200, 1010 cm^{-1}

^1H NMR : δ 4.44 (1H, dd, $J_1 = 10$ Hz, $J_2 = 8$ Hz, $-C\underline{H}_2OCO-$), 4.24-3.90 (2H, m, $-C\underline{H}_2OCO-$; $>C\underline{H}OH$), 2.62 (2H, m), 2.20-1.14 (8H, series of m).

^{13}C NMR : δ 179.18, 70.94, 68.12, 40.29, 35.88, 35.53, 33.64, 28.35, 19.23, 14.29.

$NaBH_4$ Reduction of (122):

The reaction was performed as described in the general procedure to furnish syn : anti (39 : 61) alcohols in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

syn-alcohol:

mp. : 170-171°C

IR : 3500, 2900, 1750, 1200, 1030 cm^{-1}

^1H NMR : δ 4.47 (1H, dd, $J_1 = J_2 = 9$ Hz, $-C\underline{H}_2OCO-$), 4.17 (1H, dd, $J_1 = 4$ Hz, $J_2 = 9$ Hz, $-C\underline{H}_2OCO-$), 4.04 (1H, m, $>C\underline{H}OH$), 3.10 (1H, m, $-C\underline{H}CH_2O-$), 2.77 (1H, m), 2.63 (1H, m), 2.36-1.20 (7H, series of m).

^{13}C NMR : δ 180.01, 70.41, 67.71, 41.53, 36.76, 35.29, 28.88, 26.64, 20.29, 17.58.

Analysis : $C_{10}H_{14}O_3$: Calcd. : C, 65.91; H, 7.74
Found : C, 66.15; H, 7.72.

anti-alcohol:

mp. : 176-177°C

IR : 3475, 2900, 1740, 1200, 1000 cm^{-1}

^1H NMR : δ 4.60-4.16 (2H, series of m, $-C\underline{H}_2O-$), 3.98 (1H, m, $>C\underline{H}OH$), 2.60 (2H, m), 2.20-1.36 (8H, series of m).

^{13}C NMR : δ 179.59, 69.88, 67.88, 41.06, 36.70, 34.76, 34.64, 26.76, 21.23, 12.70.

General procedure for the Wittig alkenylation of 7-norbornanones 47a,b,e:

To a suspension of methyltriphenylphosphoniumbromide (1.07 g, 3 mmol) in dry benzene (5 ml) was added freshly sublimed sodium t-amyl oxide (165 mg, 1.5 mmol) in benzene (3 ml) and the reaction mixture was stirred for 15 min at room temperature. To the canary yellow ylide that formed

immediately was added the 7-norbornanone derivative (1 mmol) and stirring was continued for 15 min. The reaction was quenched with water (5 ml) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layer was washed and dried. The solvent was evaporated and the residue was purified by column chromatography using silica gel (70-80%).

In the case of diester 47a, 20-30% of epimerisation at C_2 center occurred resulting in a mixture of endo, endo- and exo, endo- isomers. The two isomers were separated by column chromatography using silica gel and elution with 2% ethyl acetate-hexane.

Dimethyl-7-methylenebicyclo[2.2.1]heptane-2,3-endo,endo-dicarboxylate (144a):

IR : 3050, 2950, 1730, 1200 890 cm^{-1}

^1H NMR : δ 4.66 (2H, s, olefinic), 3.64 (6H, s, -COOMe), 3.02 (2H, br s), 2.64 (2H, br s), 1.94-1.34 (4H, m).

^{13}C NMR : δ 172.59, 155.65, 98.77, 51.47, 45.70, 43.17, 23.29.

Analysis : $C_{12}H_{16}O_4$: Calcd. : C, 64.27; H, 7.19
Found : C, 64.28; H, 7.17.

2,3-endo,endo-Bis(methoxymethyl)-7-methylenebicyclo[2.2.1]-heptane (144b):

IR : 3050, 2925, 1110, 950, 880 cm^{-1}

^1H NMR : δ 4.56 (2H, s, olefinic), 3.46-3.30 (4H, m,

$\underline{CH_2}OMe$), 3.29 (6H, s, $-CH_2O\underline{Me}$), 2.44-2.12 (4H, m), 1.50 (4H, m).

^{13}C NMR : δ 158.47, 96.71, 70.24, 58.71, 42.82, 39.06, 21.35.

HRMS : $C_{12}H_{20}O_2$: Calcd. : 196.1463
Found : 196.1471.

2,3-<u>endo</u>,<u>endo</u>-Diethyl-7-methylenebicyclo[2.2.1]heptane (<u>144e</u>):

IR : 3050, 2950, 1460, 890 cm^{-1}

^1H NMR : δ 4.58 (2H, s, olefinic), 2.28 (2H, br s), 1.84 (2H, m), 1.62-1.10 (8H, m), 0.83 (6H, t, J = 6 Hz).

^{13}C NMR : δ 160.36, 95.47, 43.23, 42.23, 20.76, 19.00, 13.29.

HRMS : $C_{12}H_{20}$: Calcd. : 164.1565
Found : 164.1593.

General procedure for the epoxidation <u>144a,b,e</u>:

To a mixture of 7-methylenenorbornane derivative (0.2 mmol) and Na_2CO_3 (212 mg, 0.2 mmol) in dry dichloromethane, at ice-bath temperature, m-CPBA (0.24 mmol) was added and the reaction mixture was stirred for 30-45 min. Water was added, the organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layer was washed with saturated $NaHCO_3$ solution and dried. Solvent was evaporated and the crude residue was analysed by ^1H NMR spectroscopy.

Epoxidation of (144a):

The reaction was performed as described in the general procedure to furnish 145a : 146a (74 : 26) in 80% yield. The two isomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

145a:

IR : 2950, 1730, 1340, 1190, 1050 cm^{-1}

^1H NMR (Fig.41) : δ 3.68 (6H, s, -COOMe), 3.42 (2H, br s, >CHCOOMe), 3.02 (2H, s, $-CH_2-O-$), 2.04-1.60 (6H, m).

^{13}C NMR : δ 172.59, 72.47, 51.65, 50.41, 45.06, 41.59, 21.70.

HRMS : $C_{12}H_{16}O_5$: Calcd. : 240.0998
Found : 240.0982.

146a:

IR : 2950, 1730, 1340, 1190, 1050 cm^{-1}

^1H NMR (Fig.42) : δ 3.68 (6H, s, -COOMe), 3.24 (2H, br s, >CHCOOMe), 3.02 (2H, s), 1.95 (6H, br s).

Epoxidation of (144b):

The reaction was performed as described in the general procedure to furnish 145b : 146b (45 : 55) in 80% yield.

145b:

IR : 2925, 1200, 1110, 960 cm^{-1}

^1H NMR (300 MHz) : δ 3.58-3.39 (4H, m, $-CH_2OMe$), 3.34 (6H, s, -OMe), 2.98 (2H, s, $-CH_2-O-$), 2.73 (2H, br s, $>CH-CH_2OMe$), 1.84-161 (6H, m) (from syn : anti mix).

^{13}C NMR : δ 69.71, 58.65, 49.94, 41.12, 38.06, 20.00.

146b:

IR : 2925, 1200, 1110, 960 cm^{-1}

^{1}H NMR (300 MHz) : δ 3.58-3.39 (4H, m, $-\underline{CH_2}OMe$), 3.34 (6H, s, $-O\underline{Me}$), 3.03 (2H, s, $-C\underline{H_2}-O-$) 2.52 (2H, s, $>C\underline{H}-CH_2OMe$), 1.84-1.61 (6H, m) (from syn : anti mix).

^{13}C NMR : δ 69.88, 58.76, 50.06, 40.82, 37.53, 20.82.

Epoxidation of (144e):

The reaction was performed as described in the general procedure to furnish 145e : 146e (30 : 70) in 85% yield.

145e:

IR : 2950, 1380, 960 cm^{-1}

^{1}H NMR (300 MHz) : δ 2.98 (2H, s, $-C\underline{H_2}-O-$), 2.26 (2H, m, $>C\underline{H}-CH_2CH_3$), 1.72-1.25 (10H, m), 0.81 (6H, t, J = 7 Hz) (from syn : anti mix).

HRMS : $C_{12}H_{20}O$: Calcd. : 180.1514
Found : 180.1508.

146e:

IR : 2950, 1380, 960 cm^{-1}

^{1}H NMR (300 MHz) : δ 3.01 (2H, s, $-C\underline{H_2}-O-$), 2.04 (2H, m, $>C\underline{H}-CH_2CH_3$), 1.72-1.25 (10H, m), 0.79 (6H, t, J = 7 Hz) (from syn : anti mix).

General procedure for the hydroboration of 144a,b,e:

Into a 25 ml three necked R.B. flask equipped with a nitrogen inlet, bubbler, and mercury seal was introduced [5]

ml of dry THF and the flask was cooled to -78°C. Diborane, generated by the addition of a solution of I_2 in diglyme to a suspension of $NaBH_4$ in diglyme, was bubbled through THF for 5 min. Then, the 7-methylenenorbornane derivative (0.1 mmol) in dry THF (2 ml) was added to the diborane solution and stirring continued for 30 min at room temperature. The reaction mixture was cooled to 0°C and a solution of 3N NaOH (0.15 ml) followed by 30% H_2O_2 (0.5 ml) were added. The mixture was stirred further for 4 h at room temperature. It was then saturated with solid NaCl and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic layer was washed and dried. Removal of solvent furnished a mixture of syn- and anti-primary alcohols. The product ratios were determined by the ^1H NMR analysis of the crude reaction mixture.

Hydroboration of 144a:

The reaction was performed as described in the general procedure to furnish 147a : 148a (41 : 59) in 80% yield.

147a:

IR : 3400, 2950, 1730, 1190 cm^{-1}

^1H NMR (Fig.43) : δ 3.70 (2H, d, J = 8 Hz, $-C\underline{H}_2OH$), 3.65 (6H, s, $-COO\underline{Me}$), 3.10 (2H, br s, $>C\underline{H}COOMe$), 2.48 (2H, br s, bridgehead C$\underline{H}$), 2.07 (1H, t, J = 8 Hz, $>C\underline{H}CH_2OH$), 2.00-1.44 (4H, m, $\underline{H}_{5,6}$).

^{13}C NMR (Fig.44) : δ 173.12, 60.29, 54.06, 51.53, 44.35, 41.17, 24.64.

148a:

IR : 3400, 2950, 1730, 1190 cm^{-1}

^1H NMR (Fig.45) : δ 3.67 (2H, d, J = 8 Hz, $-C\underline{H}_2OH$), 3.66 (6H, s, $-COO\underline{Me}$), 3.04 (2H, br s, $>C\underline{H}COOMe$), 2.49 (2H, br s, bridgehead C<u>H</u>), 1.97 (1H, t, J = 8 Hz), 1.94-1.50 (4H, m).

^{13}C NMR (Fig.46) : δ 172.83, 60.41, 53.65, 51.47, 47.18, 41.17, 21.64.

Hydroboration of 144b:

The reaction was performed as described in the general procedure to furnish 147b : 148b (56 : 44) in 90% yield.

147b:

IR : 3400, 2950, 1200 cm^{-1}

^1H NMR : δ 3.68 (2H, d, J = 8 Hz, $-C\underline{H}_2OH$), 3.38 (4H, m, $-C\underline{H}_2OMe$), 3.28 (6H, s, $-O\underline{Me}$), 2.46-2.02 (4H, m), 1.92 (1H, t, J = 8 Hz, $>C\underline{H}CH_2OH$), 1.42 (4H, br s) (from syn : anti mix).

^{13}C NMR : δ 70.65 60.06, 58.71, 53.47, 40.47, 37.29, 22.88.

148b:

IR : 3400, 2950, 1200 cm^{-1}

^1H NMR : δ 3.56 (2H, d, J = 8 Hz, $-C\underline{H}_2OH$), 3.38 (4H, m, $-C\underline{H}_2OMe$), 3.27 (6H, s, $-O\underline{Me}$), 2.46-2.02 (4H, m), 1.92 (1H, t, J = 8 Hz, $>C\underline{H}CH_2OH$), 1.42 (4H, br s) (from syn : anti mix).

^{13}C NMR : δ 70.41, 60.06, 58.71, 53.47, 40.47, 19.94.

Hydroboration of 144e:

The reaction was performed as described in the general procedure to furnish 147e : 148e (68 : 32) in 90% yield.

147e:

IR : 3325, 2975, 1030 cm^{-1}

^1H NMR (500 MHz) : δ 3.74 (2H, d, J = 7.5 Hz, $-C\underline{H}_2OH$), 2.08 (2H, br s), 1.88 (1H, t, J = 7.5 Hz, $>C\underline{H}CH_2OH$), 1.81 (2H, m), 1.46-1.21 (8H, m), 0.78 (6H, t, J = 7.3 Hz, $-CH_2C\underline{H}_3$) (from syn : anti mix).

^{13}C NMR : δ 60.88, 53.00, 40.47, 39.65, 22.17, 18.94, 13.35.

Analysis : $C_{12}H_{22}O$: Calcd. : C, 79.06; H, 12.16
Found : C, 78.89; H, 12.10.

148e:

IR : 3325, 2975, 1030 cm^{-1}

^1H NMR (500 MHz) : δ 3.64 (2H, d, J = 7.5 Hz, $-C\underline{H}_2OH$), 2.08 (2H, br s), 1.88 (1H, t, J = 7.5 Hz), 1.81 (2H, m), 1.46-1.21 (8H, m), 0.78 (6H, t, J = 7.3 Hz, $-CH_2C\underline{H}_3$) (from syn : anti mix).

^{13}C NMR : δ 61.71, 53.41,43.41, 40.47, 19.17, 18.94, 13.23.

General procedure for the oxymercuration-demercuration 144a,b,e:

To a solution of 7-methylenenorbornane derivative (0.2 mmol) in THF (1 ml) was added a solution of $Hg(OAc)_2$ (0.21 mmol) in water (1 ml). Catalytic amount of acetic acid was

added and the reaction mixture was stirred at room temperature for 2-4 h. The reaction was continuously monitored by tlc till all the starting material had been consumed. The reaction mixture was then treated with 3M solution of NaOH (0.2 ml) followed by 0.5 M solution of $NaBH_4$ in 3M NaOH (0.2 ml) and stirred further for 20-30 min. The mixture was saturated with solid NaCl and extracted with ethyl acetate (3 x 5 ml). The combined organic extract was washed and dried. The solvent was removed and the crude mixture of tertiary alcohols was analysed by ^1H NMR spectroscopy.

Oxymercuration-demercuration of (144a):

The reaction was performed as described in the general procedure to furnish 67a as the major product (>95%) in 72% yield. ^1H NMR of the crude mixture did not indicate the presence of other isomer 68a. The analytical data for 67a and 68a is given under the procedure for methyllithium additions.

Oxymercuration-demercuration of (144b):

The reaction was performed as described in the general procedure to furnish 67b : 68b (40 : 60) in 90% yield. The two isomers were separated by column chromatography using silica gel and elution with 25% ethyl acetate-hexane. The analytical data for 67b and 68b is given under procedure for methyllithium additions.

Oxymercuration-demercuration of (144e):

The reaction was performed as described in the general

procedure to furnish 67e : 68e (17 : 83) in 85% yield. The analytical data for 67e and 68e is given under procedure for methyl lithium additions.

5-endo-Cyano-7-isopropylidenebicyclo[2.2.1]hept-2-ene (152a):[75]

A mixture of 6,6-dimethylfulvene (11 g, 103 mmol) and acrylonitrile (5 g, 94 mmol) was kept in the dark at room temperature for four weeks, during which time 2.5 g of pure endo isomer 152a crystallised out. The mother liquor (8 g, 70% total yield) contained a mixture of endo and exo-isomers.

mp. : 87-88°C

IR : 3050, 2900 2250, 1445, 1370, 725 cm^{-1}

^1H NMR (200 MHz) : δ 6.49 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 6.35 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 3.66 (1H, m, bridgehead C<u>H</u>), 3.43 (1H, t, J = 3 Hz, bridgehead C<u>H</u>), 2.80 (1H, ddd, J_1 = 9 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>-CN), 2.19-2.06 (1H, ddd, J_1 = 3.6 Hz, J_2 = 9.4 Hz, J_3 = 11.4 Hz, exo-<u>H</u>$_6$), 1.55 (6H, s, -<u>Me</u>), 1.41 (1H, dd, J_1 = 11.4 Hz, J_2 = 4 Hz, endo-<u>H</u>$_6$).

^{13}C NMR : δ 144.77(s), 139.42(d), 133.36(d), 122.65(s), 111.18(s), 45.06(d), 41.83(d), 32.70(t), 26.70(d), 19.53(q), 19.41(q).

2-endo-Cyano-7-isopropylidenebicyclo[2.2.1]heptane (154a):

To a solution of 152a (1.12 g, 7.04 mmol) in 5 ml of

dry ethanol was added $CuSO_4.5H_2O$ (55 mg, 0.22 mmol) and 99% hydrazine (4.5 g, 141 mmol). Oxygen gas was bubbled through the reaction mixture at room temperature with stirring for 20-30 min. Ethanol was removed under vacuum and the residue was diluted with water. The aqueous layer was extracted with ether (3 x 35 ml). The combined organic layer was washed with 5% HCl and dried. Removal of solvent and filteration through a silica gel column furnished 154a (900 mg, 80%).

mp. : 82-83°C

IR : 2950, 2275, 1450, 1380 cm^{-1}

^1H NMR (200 MHz) : δ 2.87 (1H, dd, $J_1 = J_2 = 4$ Hz, bridgehead CH), 2.63-2.76 (2H, m, bridgehead CH, >CHCN), 2.09-1.78 (2H, series of m), 1.64 (6H, s, gem-Me), 1.64-1.34 (4H, series of m).

^{13}C NMR : δ 139.30(s), 122.65(s), 117.30(s), 38.82(d), 35.64(d), 35.00(t), 29.06(d), 28.64(t), 24.35(t), 20.53(2C,q).

2-exo-cyano-7-Isopropylidenebicyclo[2.2.1]heptane (137a):

The mixture of exo- and endo-5-cyano-7-isopropylidenebicyclo[2.2.1]heptane-2-enes obtained from the Diels-Alder reaction of fulvene and acrylonitrile were partially reduced as described above for 154a using diimide. The exo- and endo-isomers were separated by column chromatography using silica gel. Elution with 2% ethyl acetate-hexane furnished first the endo-isomer (154a) further elution of the column gave exo-isomer (137a).

137a:

mp. : Low melting

IR : 2950, 2275, 1450, 1380 cm^{-1}

^1H NMR : δ 2.92 (1H, br s, bridgehead CH), 2.7 (1H, br s, bridgehead CH), 2.44 (1H, dd, $J_1 = J_2 = 6$ Hz, endo-H_2), 1.84-1.20 (7H, series of m), 1.74 (3H, s, gem-Me), 1.70 (3H, s, gem-Me).

^{13}C NMR : δ 138.01(s), 123.18(s), 118.71(s), 40.76(d), 35.29(t), 35.00(d), 30.47(d), 28.00(t), 27.88(t), 20.64(q), 20.53(q).

Methyl 7-isopropylidenebicyclo[2.2.1]hept-2-ene-5-carboxylate: 152b and 153b[75]

A solution of 6,6-dimethylfulvene (8 g, 75.4 mmol) and methyl acrylate (6.45 g, 75 mmol) in THF (9 ml) was heated at reflux temperature for 16 h. THF was removed under vacuum. The residue was charged on alumina (neutral) column. Elution with 1% ethyl acetate hexane first gave exo-isomer 153b followed by few mixture fractions and then endo-isomer 152b (total yield: 10.1 g, 70%).

endo-152b:

mp. : 44°C

IR : 3050, 2900 1725, 1440, 1380, 1030, 725 cm^{-1}

^1H NMR (200 MHz) : δ 6.34 (1H, d of 1/2 ABq, $J_1 = 6$ Hz, $J_2 = 3$ Hz, olefinic), 6.08 (1H, d of 1/2 ABq, $J_1 = 6$ Hz, $J_2 = 3$ Hz, olefinic), 3.70-3.63 (1H, m, bridgehad CH), 3.63 (3H, s, -COOMe), 3.32 (1H, m, bridgehead CH), 2.89 (1H, ddd, $J_1 = 9$ Hz, J_2

= J_3 = 4 Hz, >C<u>H</u>COOMe), 1.91 (1H, ddd, J_1 = 11.4 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.56 (3H, s, gem-<u>Me</u>), 1.54 (3H, s, gem-<u>Me</u>), 1.50 (1H, dd, J_1 = 11.4 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$).

^{13}C NMR : δ 171.77, 147.42, 138.18, 132.89, 108.41, 51.47, 45.18, 42.47, 42.23, 29.70, 19.35.

<u>exo</u>-<u>153b</u>:

IR : 3050, 2900, 1725, 1440, 1380, 1030, 725 cm^{-1}

^{1}H NMR (200 MHz) : δ 6.34-6.22 (2H, m, olefinic), 3.66 (3H, s, -COO<u>Me</u>), 3.56 (1H, st s, bridgehead C<u>H</u>), 3.33 (1H, br s, bridgehead C<u>H</u>), 2.30 (1H, dd, J_1 = 9.4 Hz, J_2 = 4.4 Hz, >C<u>H</u>COOMe), 1.94 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.4 Hz), 1.57 (3H, s, gem-<u>Me</u>), 1.55 (3H, s, gem-<u>Me</u>), 1.45 (1H, dd, J_1 = 9.4 Hz, J_2 = 11.4 Hz)

^{13}C NMR : δ 175.59, 145.54, 138.48, 135.94, 110.30, 51.59, 45.65, 43.29, 41.47, 30.25, 19.53.

Methyl 7-isopropylidenebicyclo[2.2.1]heptane-2-<u>endo</u>-carboxylate <u>154b</u>:

To a solution of <u>152b</u> (600 mg, 3.13 mmol) in 5 ml of dry ethanol was added $CuSO_4.5H_2O$ (30 mg, 0.12 mmol) and hydrazine (2 g, 62.5 mmol). Oxygen was bubbled through the reaction mixture at room temperature with stirring for 20-30 min. Ethanol was removed under vacuum and the residue was diluted with water. The aqueous layer was extracted with ether (3 x 30 ml). The combined organic layer was washed with 5% HCl and dried. Removal of solvent and filteration

through a small silica gel column furnished 154b (500 mg, 83%).

IR : 2900, 1730, 1440, 1180 cm^{-1}

^1H NMR (200 MHz) : δ 3.69 (3H, s, -COOMe), 2.90 (1H, m, bridgehead CH), 2.82-2.69 (1H, m, >CHCOOMe), 2.62 (1H, m, bridgehead CH), 1.80-1.30 (6H, series of m), 1.67 (3H, s, gem-Me), 1.64 (3H, s, gem-Me).

^{13}C NMR : δ 175.16(s), 142.44(s), 114.32(s), 51.42(q), 44.88(d), 39.64(d), 36.43(d), 31.93(t), 28.78(t), 24.35(t), 20.50(2C,q).

General procedure for bromination: bromination of 154a:

To a solution of 154a (66 mg, 0.41 mmol) in 10% aqueous dimethoxyethane (3 ml) at 0°C N-bromosuccinimide (88 mg, 0.49 mmol) was added and the reaction mixture was stirred for 10-15 min at ice-bath temperature. The reaction mixture was diluted with ether and water. The organic layer was separated, and aqueous layer was extracted twice with ether. The combined organic layers were washed with 10% sodium bisulfite and dried. The solvent was removed under reduced pressure and the crude mixture (98 mg, 100%) was analysed by high resolution ^1H NMR spectroscopy. As it was observed that some allylic rearrangement was taking place at elevated temperatures, all the above processes were carried out at ~5-10°C. The ratio of syn-155a and anti-156a allyl bromides was found to be 72 : 28 based on ^1H NMR integration.

155a:

bp. : 110-120°C/0.3 mm

IR : 2925, 2230, 1450, 900, 820 cm^{-1}

^1H NMR (200 MHz) : δ 5.11 (1H, s, olefinic), 4.99 (1H, m, olefinic), 3.52 (1H, m, >C<u>H</u>CN), 2.78-2.52 (3H, series of m), 1.93 (3H, s, -(<u>Me</u>)C=CH_2), 1.93-1.35 (5H, series of m).

^{13}C NMR : δ 143.65, 122.18, 114.47, 80.00, 47.35, 44.53, 35.82, 30.76, 26.17, 22.23, 19.23.

Analysis : $C_{11}H_{14}BrN$: Calcd. : C, 55.01; H, 5.88, N, 5.83
Found : C, 54.89; H, 5.78, N, 5.78.

<u>156a</u>:

bp. : 110-120°C/0.3 mm

IR : 2925, 2230, 1450, 900, 820 cm^{-1}

^1H NMR (200 MHz) : δ 5.11 (1H, s, olefinic), 4.99 (1H, m, olefinic), 2.74 (1H, m), 2.58 (1H, m), 2.32-1.50 (7H, series of m), 1.93 (3H, s, -(<u>Me</u>)C=CH_2).

Bromination of <u>154b</u>:

Bromination <u>154b</u> was carried out as described in the general procedure to furnish <u>155b</u> : <u>156b</u> (59 : 41) in 95% yield. The major stereoisomer was separated by preparative layer chromatography on silica gel.

<u>155b</u>:

bp. : 110-120°C/0.3 mm

IR : 2925, 1725, 1430, 1200, 900 cm^{-1}

^1H NMR (200 MHz) : δ 5.11 (1H,, s, olefinic), 5.95 (1H, m, olefinic), 3.71 (3H, s, -COO<u>Me</u>), 3.60-3.46 (1H, m, -C<u>H</u>COO<u>Me</u>), 2.77 (1H, m), 2.52 (1H, m), 2.31

(1H, m), 1.94 (3H, m, -(Me)C=CH_2), 1.94-1.18 (4H, series of m), 0.92-0.82 (1H, m).

General procedure for the dichlorocarbene addition to 154a,b and 152a,b:

A solution of 7-isopropylidenenorbornane derivative (1.5 mmol) and sodium trichloroacetate (30 mmol) in 50 ml of tetrachloroethylene-DME (1 : 1) was heated at the reflux temperature for 10-48 h. The reaction mixture was cooled, diluted with water and extracted with ether (3 x 35 ml). The combined organic layer was washed with saturated sodium bicarbonate, 10% ammonium chloride, and brine prior to drying. After the removal of solvent, the residue was purified by column chromatography using silica gel (elution with 1-2% ethyl acetate-hexane). The product ratios of syn- and anti-adducts were determined from the isolated yields of adducts and ^{1}H NMR or glc analysis of mixture.

Dichlorocarbene addition to 154a:

The reaction was performed as described in the general procedure to furnish 157a : 158a (78 : 22) in 85% yield.

157a:

mp. : 90°C

IR : 2925, 2250, 1450, 1380, 840 cm^{-1}

^{1}H NMR (200 MHz) : δ 3.22-3.09 (1H, m, >CHCN), 2.52-2.34 (1H, m), 2.27 (1H, m), 2.19-1.99 (2H, m), 1.81-1.50 (4H, series of m), 1.31 (6H, s, gem-Me).

^{13}C NMR : δ 121.71, 70.95, 52.29, 42.29, 38.94, 34.42, 29.29, 29.00, 25.00, 19.53, 19.41.

158a:

mp. : 136°C

IR : 2925, 2250, 1450, 1380, 840 cm^{-1}

^1H NMR (200 MHz) : δ 2.88-2.76 (1H, m, >CHCN), 2.31-1.95 (6H, series of m), 1.75-1.52 (2H, series of m), 1.31 (3H, s, gem-Me), 1.30 (3H, s, gem-Me).

^{13}C NMR : δ 121.30, 70.71, 52.18, 42.20, 38.88, 35.18, 29.82, 28.94, 28.23, 24.18, 19.53.

Dichlorocarbene addition to 154b:

The reaction was performed as described in the general procedure to furnish 157b : 158b (60 : 40) in 76% yield.

157b:

IR : 2950, 1730, 1305, 1205, 845 cm^{-1}

^1H NMR (200 MHz) : δ 3.70 (3H, s, -COOMe), 3.26-3.15 (1H, m, >CHCOOMe), 2.31 (1H, m, bridgehead CH), 2.21-1.44 (7H, series of m), 1.30 (3H, s, gem-Me), 1.29 (3H, s, gem-Me).

Dichlorocarbene addition to 152a:

The reaction was performed as described in the general procedure to furnish 163a : 164a (35 : 65) in 80% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 5% ethyl acetate-hexane.

163a:

mp. : 91°C

IR : 2950, 2250, 1460, 1380, 840, 730 cm^{-1}

^1H NMR (200 MHz) (Fig.49) : δ 6.44 (1H, d of 1/2 ABq, J_1 = 5.6 Hz, J_2 = 3 Hz), 6.31 (1H, d of 1/2 ABq, J_1 = 5.6 Hz, J_2 =

3 Hz), 3.22-3.12 (1H, m, >C<u>H</u>CN), 3.01 (1H, br s, bridgehead C<u>H</u>), 2.80 (1H, br s, bridgehead C<u>H</u>), 2.56-2.41 (1H, m, <u>exo</u>-<u>H</u>$_6$), 1.52 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$), 1.24 (3H, s, gem-<u>Me</u>), 1.23 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 138.77, 132.83, 121.83, 70.76, 59.41, 47.79, 44.06, 31.88, 29.29, 26.47, 20.35, 20.23.

<u>164a</u>:

mp. : 151°C

IR : 2950, 2250, 1460, 1380, 840, 730 cm^{-1}

^{1}H NMR (200 MHz) (Fig.50) : δ 6.56 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 6.43 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 3.10 (1H, m, bridgehead C<u>H</u>), 2.92-2.83 (2H, m, >C<u>H</u>CN; bridgehead C<u>H</u>), 2.21 (1H, ddd, J_1 = 13 Hz, J_2 = 9.4 Hz, J_3 = 3.6 Hz, <u>exo</u>-<u>H</u>$_6$), 1.56 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$), 1.24 (3H, s, gem-<u>Me</u>), 1.22 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 138.65(d), 132.71(d), 121.42(s), 69.29(s), 60.65(s), 47.70(d), 44.53(d), 32.64(t), 30.00(s), 27.74(d), 18.41(2C, q).

Dichlorocarbene addition to <u>152b</u>:

The reaction was performed as described in the general procedure to furnish <u>163b</u> : <u>164b</u> (34 : 66) in 70% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 2% ethyl acetate-hexane.

163b:

mp. : 56°C

IR : 2950, 1730, 1200 cm^{-1}

^1H NMR (200 MHz) : δ 6.25 (1H, d of 1/2 ABq, J_1 = 5.4 Hz, J_2 = 3 Hz, olefinic), 6.04 (1H, d of 1/2 ABq, J_1 = 5.6 Hz, J_2 = 3 Hz, olefinic), 3.64 (3H, s, -COO<u>Me</u>), 3.25 (1H, ddd, J_1 = 9 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>COOMe), 2.99 (1H, m, bridgehead C<u>H</u>), 2.68 (1H, m, bridgehead C<u>H</u>), 2.29 (1H, ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-$\underline{H}_6$), 1.62 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-$\underline{H}_6$), 1.21 (3H, s, gem-<u>Me</u>), 1.20 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 174.42, 137.54, 132.72, 71.06, 60.18, 51.70, 47.18, 44.29, 42.41, 28.94, 20.47, 20.35.

164b:

mp. : 70°C

IR : 2950, 1730, 1180 cm^{-1}

^1H NMR (200 MHz) : δ 6.36 (1H, d of 1/2 ABq, J_1 = 5.4 Hz, J_2 = 3 Hz, olefinic), 6.12 (1H, d of 1/2 ABq, J_1 = 5.6 Hz, J_2 = 2.8 Hz, olefinic), 3.61 (3H, s, -COO<u>Me</u>), 3.05 (1H, m, bridgehead C<u>H</u>), 2.93 (1H, ddd, J_1 = 9.2 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>COOMe), 2.75 (1H, m, bridgehead C<u>H</u>), 1.96 (1H, ddd, J_1 = 12.8 Hz, J_2 = 9.2 Hz, J_3 = 3.6 Hz, <u>exo</u>-$\underline{H}_6$), 1.62 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz, <u>endo</u>-$\underline{H}_6$), 1.22 (3H, s, gem-<u>Me</u>), 1.19 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 173.89, 137.42, 132.59, 70.06, 61.35, 51.70,

47.59, 44.70, 43.06, 29.82, 29.50, 18.58.

General procedure for the photooxygenation of 154a,b and 152a,b:

In a small irradiation vessel fitted with an outer jacket for cold water circulation was placed olefin (0.38 mmol), methylene blue (15 mg) and 30 ml of dry dichloromethane. The solution was irradiated with a 500 ml tungsten lamp under a slow stream of bubbling oxygen for 10-12 h. The solvent was removed under vacuum at room temperature and the residue was charged on a small silica gel column. The column was first eluted with 15-20% ethyl acetate-hexane till the unreacted starting material completely eluted out. It was then washed with 50% ethyl acetate-hexane. The hydroperoxide thus obtained was concentrated under vacuum at room temperature and then dissolved in 3 ml dry methanol. The methanolic solution was treated with sodium borohydride (80-100 mg) and stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in ether and water. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed and dried.

Photooxygenation of 154a:

The photooxygenation of 154a (52 mg, 0.32 mmol) was performed as described in the general procedure to 159a and 160a. The crude mixture (75%, based on starting material

recovery) was analysed by high resolution ^{1}H NMR and glc. The ratios of syn : anti obtained by two methods were found to be 78 : 22 (^{1}H NMR) and 78.5 : 21.5 (glc). The major isomer 159a was separated by preparative layer chromatography on silica gel.

159a:

bp. : 130-140°C/0.3 mm

IR : 3350, 2950, 2250, 1040, 900 cm^{-1}

^{1}H NMR (200 MHz) : δ 5.05 (1H, m, olefinic), 5.02 (1H,, m, olefinic), 3.42-3.30 (1H, m, >CHCN), 2.59-2.42 (1H, m), 2.33 (1H, m, bridgehead CH), 2.15 (1H, m, bridgehead CH), 1.87 (3H, s, -(Me)C=CH_2, 1.87-1.25 (5H, series of m).

^{13}C NMR : δ 144.26, 123.07, 113.91, 88.25, 44.78, 41.46, 34.33, 28.94, 27.21, 22.95, 18.81.

Analysis : $C_{11}H_{15}NO$: Calcd. : C, 74.54; H, 8.53; N, 7.90
Found : C, 74.45; H, 8.50, N, 7.85.

Photooxygenation of 154b:

Photooxygenation of 154b (42 mg, 0.22 mmol) was performed as described in the general procedure to furnish 159b : 160b (62 : 38) in 81% yield. The two stereoisomer were separated by preparative layer chromatography on silica gel.

159b:

bp. : 100-110°C/0.3 mm

IR : 3450, 3070, 2950, 1720, 1180 cm^{-1}

^1H NMR (200 MHz) (Fig.47) : δ 5.03 (1H, m, olefinic), 4.96 (1H, m, olefinic), 3.69 (3H, s, -COOMe), 3.42-3.32 (1H, m, >CHCOOMe), 2.39 (1H, t, J = 4 Hz, bridgehead CH), 2.27-2.04 (2H, series of m), 1.87 (3H, s, (-Me)C=CH_2), 1.87-1.47 (4H, series of m), 1.37-1.17 (2H, series of m).

^{13}C NMR : δ 176.30 145.24, 113.12, 89.12, 51.53, 45.12, 44.23, 41.65, 30.47, 27.11, 22.76, 18.70.

Analysis : $C_{12}H_{18}O_3$: Calcd. : C, 68.54; H, 8.63
Found : C, 68.44; H, 8.58.

160b:

bp. : 100-110°C/0.3 mm

IR : 3450, 3070, 2950, 1720, 1180 cm^{-1}

^1H NMR (200 MHz) (fig.48) : δ 5.12 (1H, m, olefinic), 5.01 (1H, m, olefinic), 3.68 (3H, s, -COOMe), 2.90-2.78 (1H, m, >CHCOOMe), 2.39 (1H, m, bridgehead CH), 2.11 (1H, m, bridgehead CH), 2.06-1.96 (2H, m), 1.90 (3H, s, -(Me)C=CH_2, 1.89-1.23 (5H, series of m).

^{13}C NMR : δ 175.13, 145.11, 113.42, 88.49, 51.53, 44.88, 43.18, 41.58, 29.93, 28.03, 23.39, 19.07.

Photooxygenation of 152a:

The photooxygenation of 152a was performed as described in the general procedure to furnish 165a : 166a (96 : 4, ^1H NMR and 96.5 : 3.5, glc) in 70% yield. Crystallization (CH_2Cl_2-hexane) of crude reaction mixture furnished analytically pure major isomer 165a.

165a:

mp. : 107-108°C

IR : 3400, 2950, 2250, 1100, 740 cm^{-1}

^1H NMR (200 MHz) : δ 6.27 (1H, dd, of 1/2 ABq, J_1 = 6Hz, J_2 = 3.2 Hz, J_3 = 1 Hz, olefinic), 6.13 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3.2 Hz, olefinic), 4.91 (2H, m, -(Me)C=C$\underline{H}_2$), 3.33 (1H, ddd, J_1 = 9 Hz, J_2 = J_3 = 3.8 Hz, >C$\underline{H}$CN), 3.07 (1H, m, bridgehead C$\underline{H}$), 2.86 (1H, t, J = 3.6 Hz, bridgehead C$\underline{H}$), 2.56 (1H, ddd, J_1 = 12.8 Hz, J_2 = 9.2 Hz, J_3 = 4 Hz, exo-$\underline{H}_6$), 1.76 (3H, m, -$\underline{Me}$), 1.39 (1H, dd, J_1 = 11.6 Hz, J_2 = 4 Hz, endo-$\underline{H}_6$.

^{13}C NMR : δ 145.00(s), 137.97(d), 132.07(d), 122.99(s), 114.35(t), 93.57(s), 51.44(d), 48.26(d), 31.29(t), 26.34(d), 20.97(q).

Analysis : $C_{11}H_{13}NO$: Calcd. : C, 75.40; H, 7.48; N, 7.99
Found : C, 75.32; H, 7.50; N, 8.03.

Photooxygenation of 152b:

The photooxygenation of 152b was performed as described in the general procedure to furnish 165b and 166b. The crude mixture (80%, based on starting material recovery) was analysed by high resolution ^1H NMR and glc. The ratios of syn : anti obtained by two methods were found to be 95 : 5 (^1H NMR) and 92 : 8 (glc).

165b:

bp. : 100-110°C/03 mm

IR : 3400, 2950, 1730, 1100, 1080 cm^{-1}

^1H NMR (200 MHz) : δ 6.12 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3.4 Hz, olefinic), 5.88 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3.2 Hz, olefinic), 4.91 (1H,m, olefinic), 4.87 (1H,m, olefinic), 3.64 (3H, s, -COO<u>Me</u>), 3.39 (1H, ddd, J_1 = 8.8 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>COOMe), 3.10 (1H, m, bridgehead C<u>H</u>), 2.77 (1H, m), 2.30 (1H, ddd, J_1 = 12.4 Hz, J_2 = 9 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.77 (3H, s, -<u>Me</u>), 1.53 (1H, dd, J_1 = 11.4 Hz, J_2 = 4 Hz, <u>endo</u>-<u>H</u>$_6$).

^{13}C NMR : δ 175.55(s), 146.22(s), 136.71(d), 131.91(d), 113.43(t), 94.12(s), 51.52(d), 51.30(q), 48.27(d), 42.08(d), 27.89(t), 21.01(q).

Analysis : $C_{12}H_{16}O_3$: Calcd. : C, 69.21; H, 7.74
Found : C, 69.15; H, 7.70.

<u>166b</u>:

IR : 3400, 2950, 1730, 1100, 1080 cm^{-1}

^1H NMR (200 MHz) : δ 6.32 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3.2 Hz, olefinic), 6.08 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 5.09 (1H, m, olefinic), 5.06 (1H, m, olefinic), 3.24 (1H, m, bridgehead C<u>H</u>), 3.03 (1H, ddd, J_1 = 9.2 Hz, J_2 = J_3 = 4.4 Hz, >C<u>H</u>COOMe), 2.94 (1H, m, bridgehead C<u>H</u>), 2.04 (1H, m, <u>exo</u>-<u>H</u>$_6$), 1.82 (3H, s, -<u>Me</u>), 1.37 (1H, dd, J_1 = 12.4 Hz, J_2 = 4.4 Hz, <u>endo</u>-<u>H</u>$_6$).

General procedure for the epoxidation of 154a,b and 152a,b:

To a mixture of olefin (0.42 mmol) and Na_2CO_3 (100 mg, 0.94 mmol) in dry dichloromethane at ice-bath temperature, m-CPBA (130 mg, 60%, 0.44 mmol) was added. The reaction mixture was stirred for 30-45 min at ice-bath temperature. Water was added, the organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate solution and dried. After the removal of solvent, the crude residue was analyzed by ^1H NMR spectroscopy.

Epoxidation of 154a:

The reaction was performed as described in the general procedure to furnish 161a : 162a (77 : 23) in quantitative yield. The major isomer 161a was separated by column chromatography using silica gel and elution with 5% ethyl acetate-hexane.

161a:

bp. : 100-110°C/0.3 mm

IR : 2950, 2250, 1380 cm^{-1}

^1H NMR (200 MHz) : δ 3.20-3.08 (1H, m, >C<u>H</u>-CN), 2.48-2.31(1H, m), 2.04-1.47 (7H, series of m), 1.37 (3H, s, gem-<u>Me</u>), 1.36 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 122.06, 80.65, 62.35, 39.23, 35.42, 33.64, 28.41, 26.06, 22.00, 21.23(2C).

Analysis : $C_{11}H_{15}NO$: Calcd. : C, 74.54; H, 8.53; N, 7.90
Found : C, 74.45; H, 8.45, N, 7.85.

Epoxidation of 154b:

The reaction was performed as described in the general procedure to furnish 161b : 162b (62 : 38) in 95% yield. The major stereoisomer 161b was separated by column chromatography using silica gel and elution with 10% ethyl acetate-hexane.

161b:

bp. : 100-110°C/0.3 mm

IR : 2925, 1725, 1200 cm^{-1}

^1H NMR (200 MHz) : δ 3.70 (3H, s, -COOMe), 3.27-3.15 (1H, m, >CHCOOMe), 2.14-2.04 (1H, m), 1.95-1.30 (7H, series of m), 1.39 (3H, s, gem-Me), 1.37 (3H, s, gem-Me).

^{13}C NMR : δ 175.18, 82.24, 62.24, 51.65, 43.76, 39.59, 35.94, 30.23, 26.11, 21.94, 21.35.

Analysis : $C_{11}H_{18}O_3$: Calcd. : C, 68.54; H, 8.63
Found : C, 68.60; H, 8.65.

Epoxidation of 152a:

The reaction was performed as described in the general procedure to furnish 167a : 168a (>90 : traces) in 95% yield. The ^1H NMR spectrum of the crude reaction mixture indicated the presence of only syn-isomer 167a.

167a:

mp. : 92-93°C

IR : 2975 2250, 1390 740 cm^{-1}

^1H NMR (200 MHz) : δ 6.47 (1H, dd of 1/2 ABq, J_1 = 6.2 Hz, J_2 = 3.4 Hz, J_3 = 1 Hz, olefinic), 6.33 (1H, dd of

1/2 ABq, J_1 = 6.2 Hz, J_2 = 3.4 Hz, J_3 = 1 Hz, olefinic), 3.17 (1H, ddd, J_1 = 9.4 Hz, J_2 = J_3 = 4 Hz, >C<u>H</u>CN), 2.85 (1H, m, bridgehead C<u>H</u>), 2.62 (1H, t, J = 3.6 Hz, bridgehead C<u>H</u>), 2.47 (1H, ddd, J_1 = 11.8 Hz, J_2 = 9.4 Hz, J_3 = 4 Hz, <u>exo</u>-H_6), 1.52 (1H, dd, J_1 = 11.8 Hz, J_2 = 4 Hz, <u>endo</u>-H_6), 1.33 (3H, s, gem-<u>Me</u>), 1.32 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 137.65(d), 131.71(d), 122.24(s), 85.82(s), 63.53(s), 45.70(d), 42.06(d), 31.12(t), 26.00(d), 21.88(q), 21.42(q).

Analysis : $C_{11}H_{13}NO$: Calcd. : C, 75.40; H, 7.48, N, 7.99
Found : C, 75.25; H, 7.45, N, 7.96.

Epoxidation of <u>152b</u>:

The reaction was performed as described in the general procedure to furnish <u>167b</u> : <u>168b</u> (>85 : <15) in 95% yield. The isomers were separated by preparative layer chromatography on silica gel.

<u>167b</u>:

bp. : 100°C/0.5 mm

IR : 3075, 2975, 1735, 1200, 720 cm^{-1}

^1H NMR (200 MHz) (Fig.51) : δ 6.32 (1H, dd of 1/2 ABq, J_1 = 6.2 Hz, J_2 = 3.2 Hz, J_3 = 0.8 Hz, olefinic), 6.08 (1H, dd of 1/2 ABq, J_1 = 6.2 Hz, J_2 = 3.2 Hz, J_3 = 0.8 Hz, olefinic), 3.65 (3H, s, -COO<u>Me</u>), 3.26 (1H, ddd, J_1 = 9.2 Hz, J_2 = J_3 = 4.2 Hz, >C<u>H</u>COOMe), 2.86 (1H, m, bridgehead C<u>H</u>), 2.53 (1H, t, J = 3.6

Hz, bridgehead C<u>H</u>), 2.25 (1H, ddd, J_1 = 12 Hz, J_2 = 9.4 Hz, J_3 = 4 Hz, <u>exo</u>-<u>H</u>$_6$), 1.63 (1H, dd, J_1 =12 Hz, J_2 = 4.4 Hz, <u>endo</u>-<u>H</u>$_6$), 1.34 (3H, s, gem-<u>Me</u>), 1.31 (3H, s, gem-<u>Me</u>).

^{13}C NMR : δ 174.83(s), 136.30(d), 131.53(d), 86.88(s), 63.29(s), 51.65(q), 45.53(d), 42.23(d), 41.65(d), 28.06(t), 21.64(q), 21.52(q).

Analysis : $C_{12}H_{16}NO_3$: Calcd. : C, 69.21; H, 7.74
Found : C, 69.28; H, 7.78.

<u>168b</u>:

bp. : 100°C/0.5 mm

IR : 3075, 2975, 1735, 1200, 720 cm^{-1}

^{1}H NMR (200 MHz) (Fig.52) : δ 6.37 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 3 Hz, olefinic), 6.12 (1H, d of 1/2 ABq, J_1 = 6 Hz, J_2 = 2.4 Hz, olefinic), 3.66 (3H, s, -COO<u>Me</u>), 3.02-2.92 (2H, >C<u>H</u>COOMe and bridgehead C<u>H</u>), 2.65 (1H, t, J = 3.4 Hz), 2.08-1.93 (1H, m, <u>exo</u>-<u>H</u>$_6$), 1.67-1.50 (1H, m, <u>endo</u>-<u>H</u>$_6$), 1.34 (3H, s, gem-<u>Me</u>), 1.31 (3H, s, gem-<u>Me</u>).

V. SPECTRA

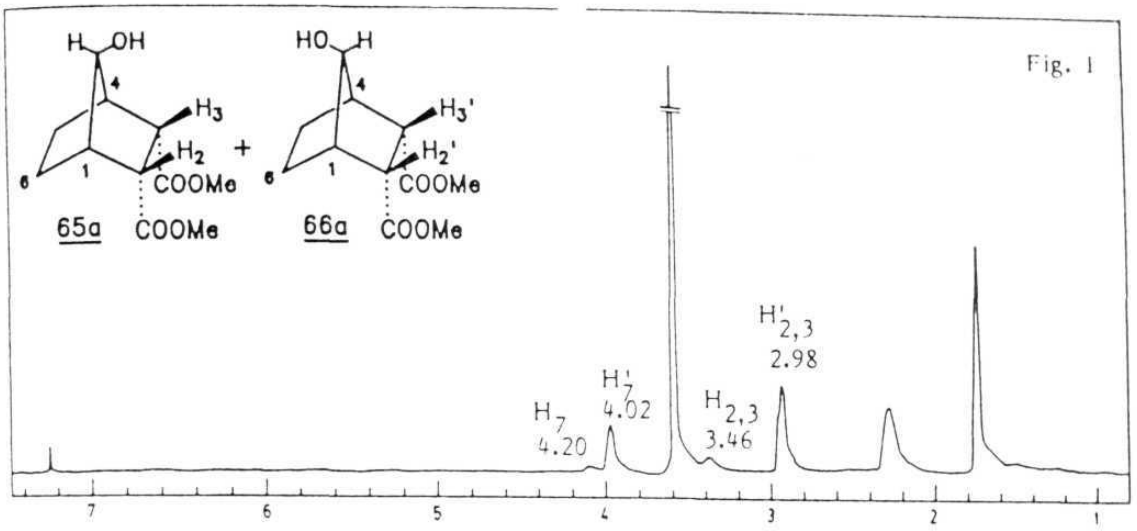


Fig. 1

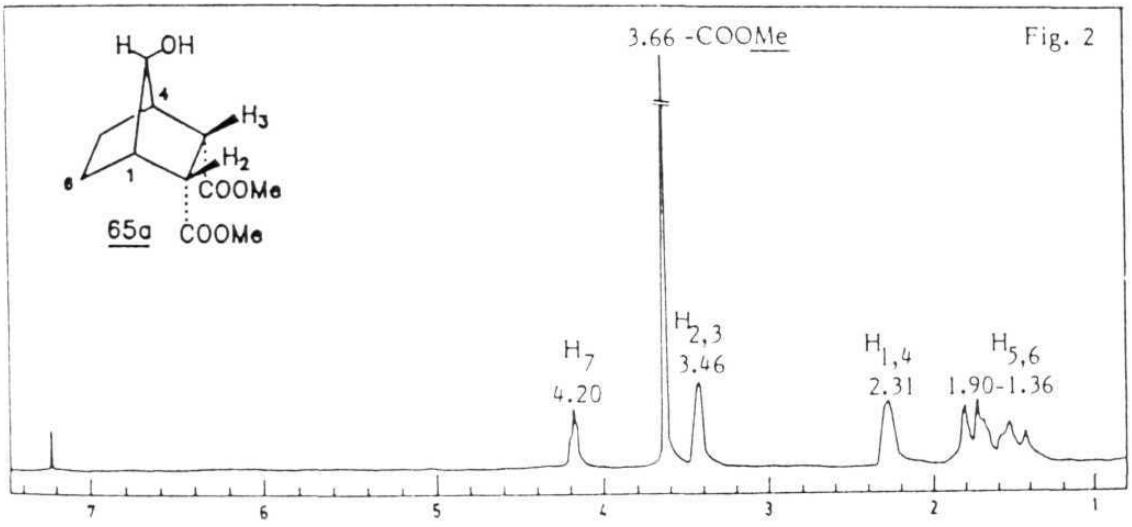


Fig. 2

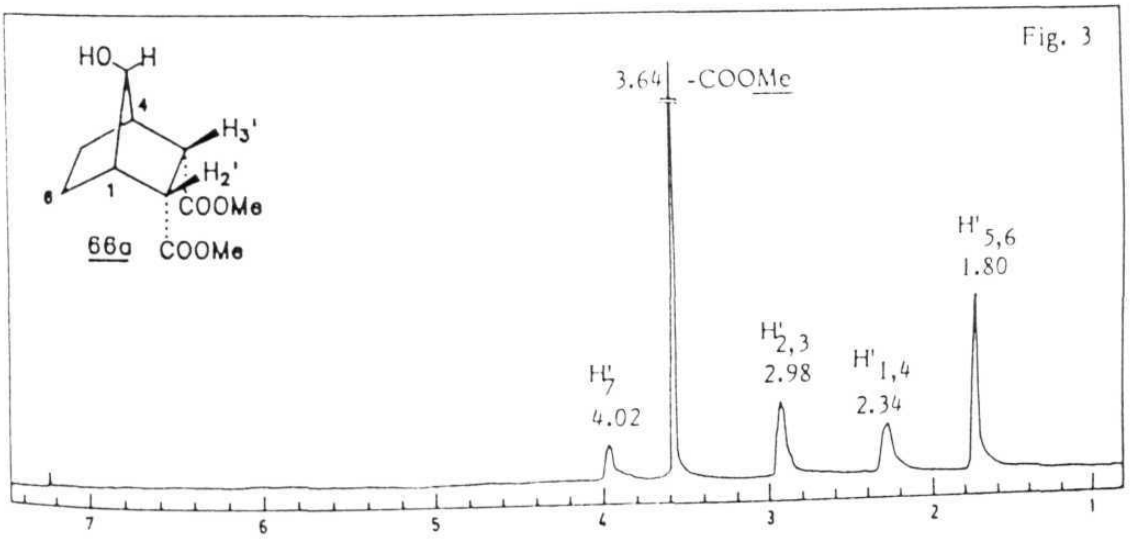
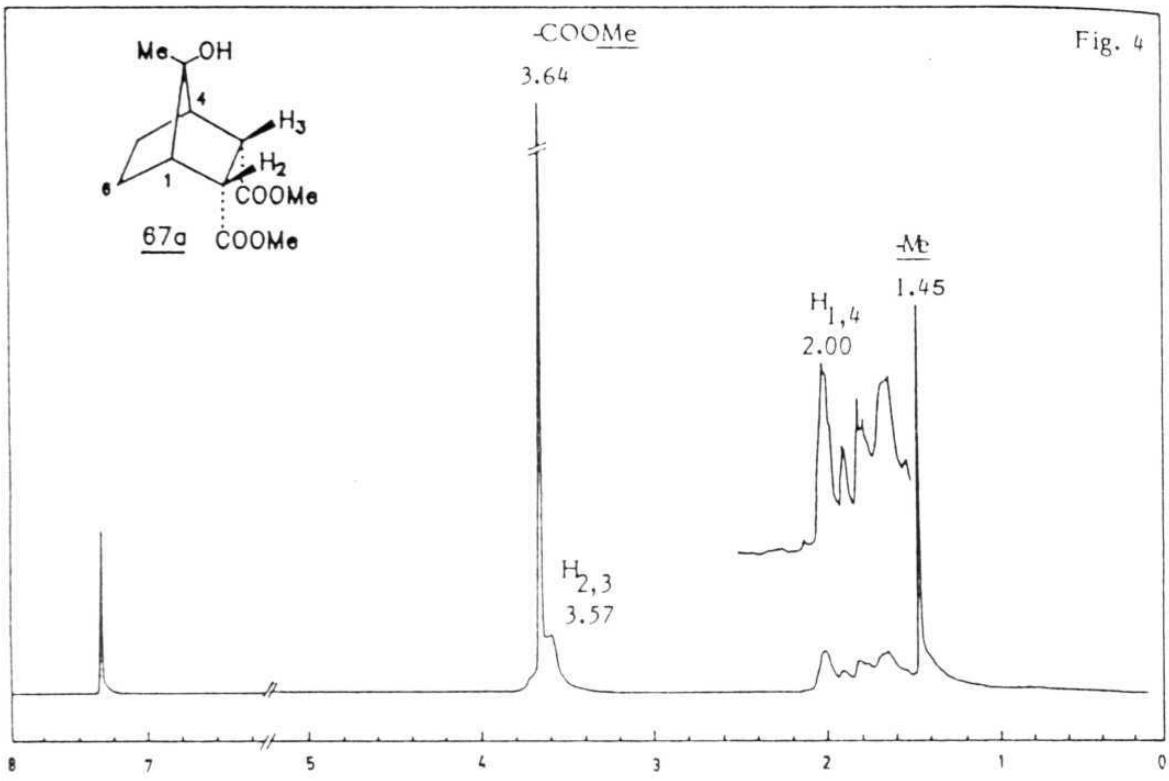


Fig. 3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COOMe
67a
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7
5
4
3
2
1
0

Fig. 4

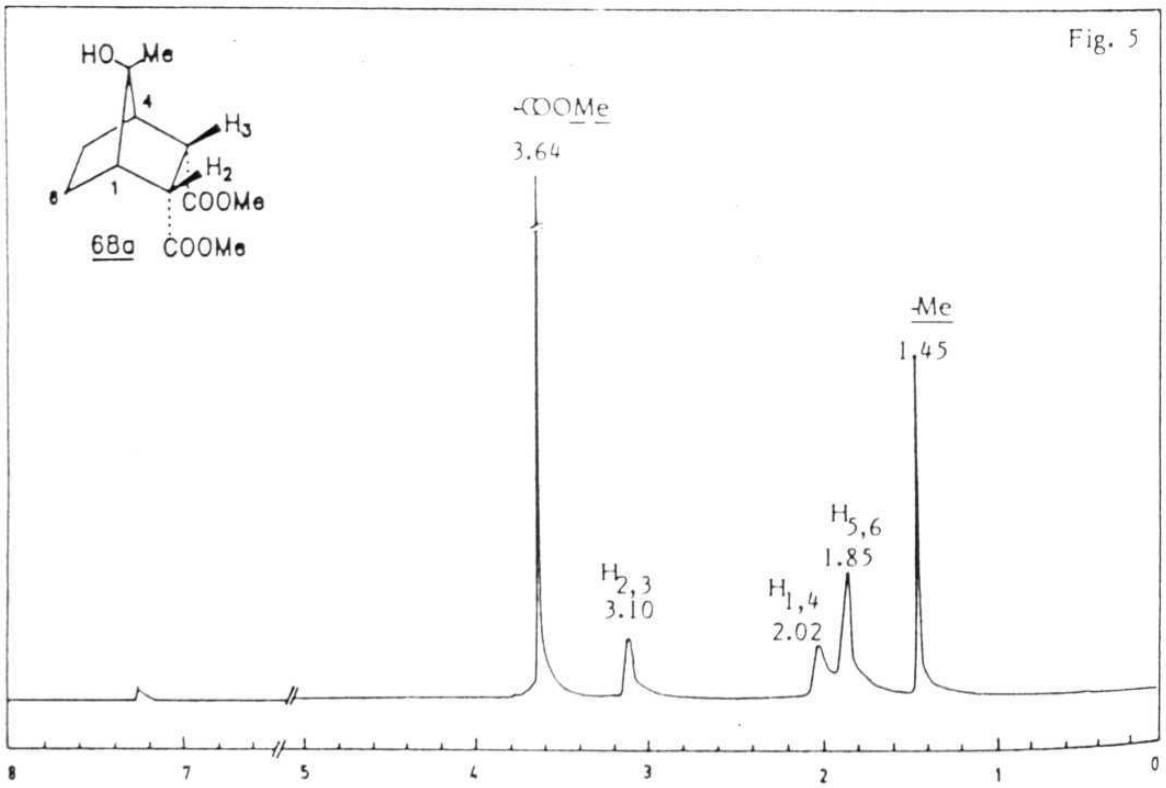

HO
Me
4
H3
H2
6
1
COOMe
68a
COOMe
-COOMe
3.64
-Me
1.45
H5,6
1.85
H2,3
3.10
H1,4
2.02
8
7
5
4
3
2
1
0

Fig. 5

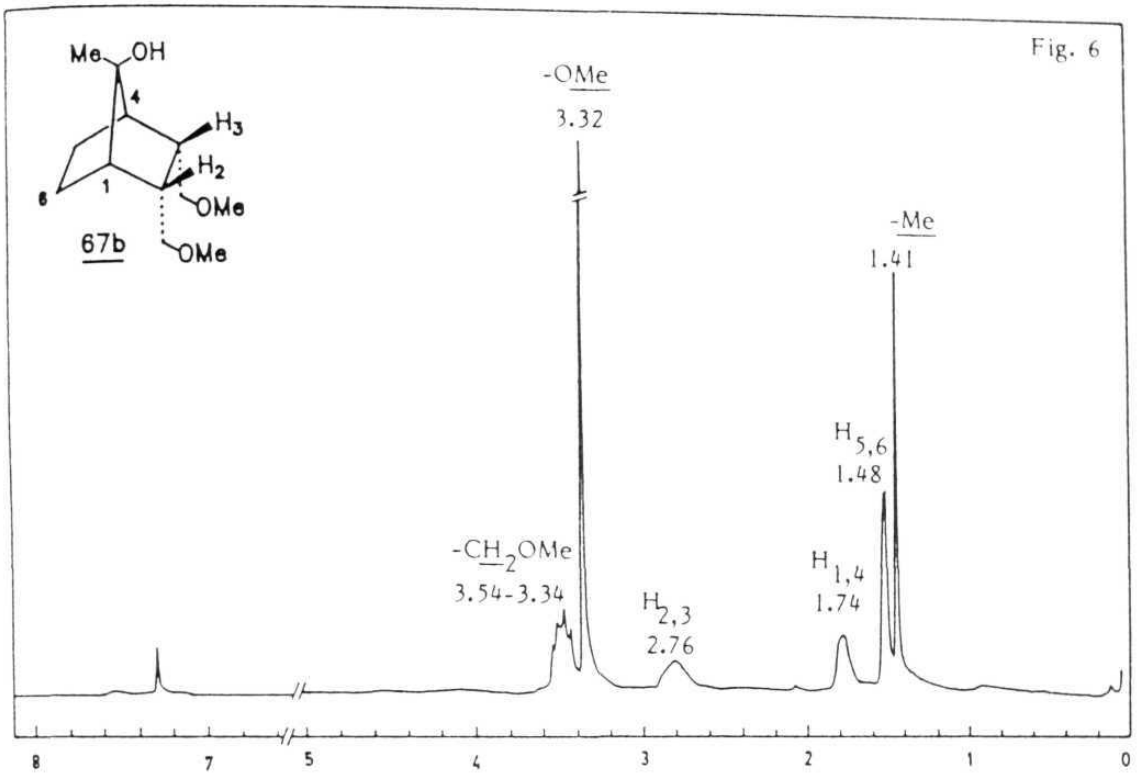

Me OH
4
H3
H2
6
1
OMe
67b
OMe
-OMe
3.32
-Me
1.41
H5,6
1.48
-CH2OMe
3.54-3.34
H1,4
1.74
H2,3
2.76
8
7
5
4
3
2
1
0

Fig. 6

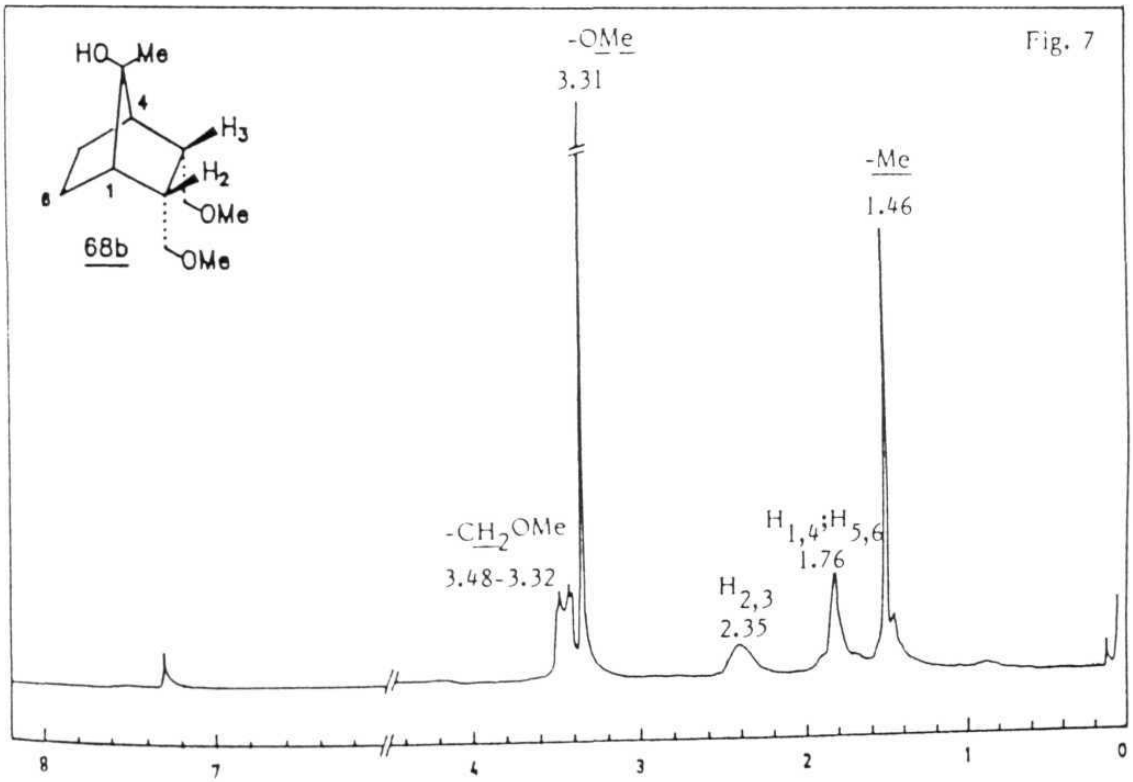

HO Me
4
H3
H2
6
1
OMe
68b
OMe
-OMe
3.31
-Me
1.46
-CH2OMe
3.48-3.32
H1,4;H5,6
1.76
H2,3
2.35
8
7
4
3
2
1
0

Fig. 7

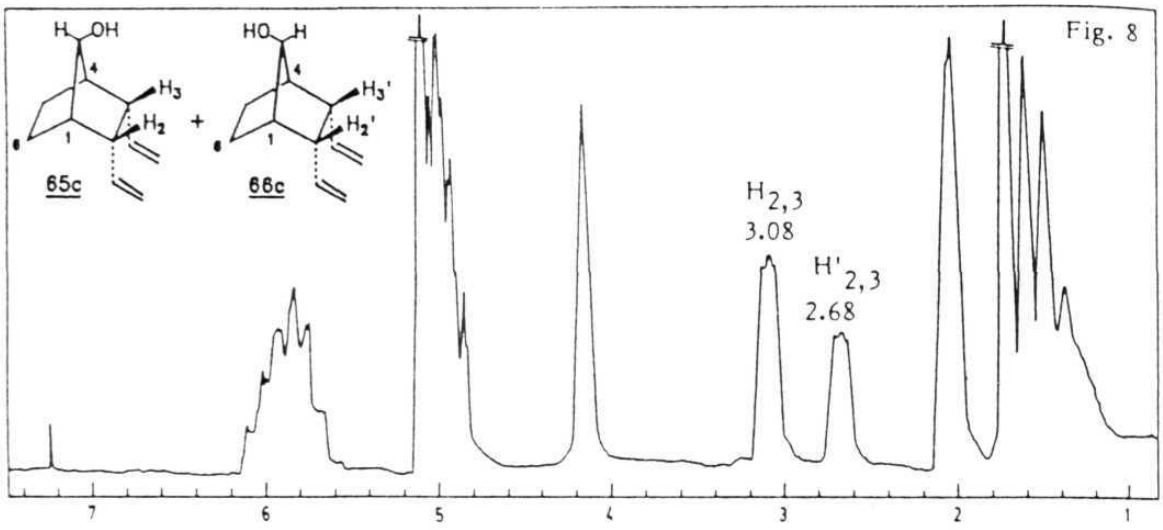


Fig. 8

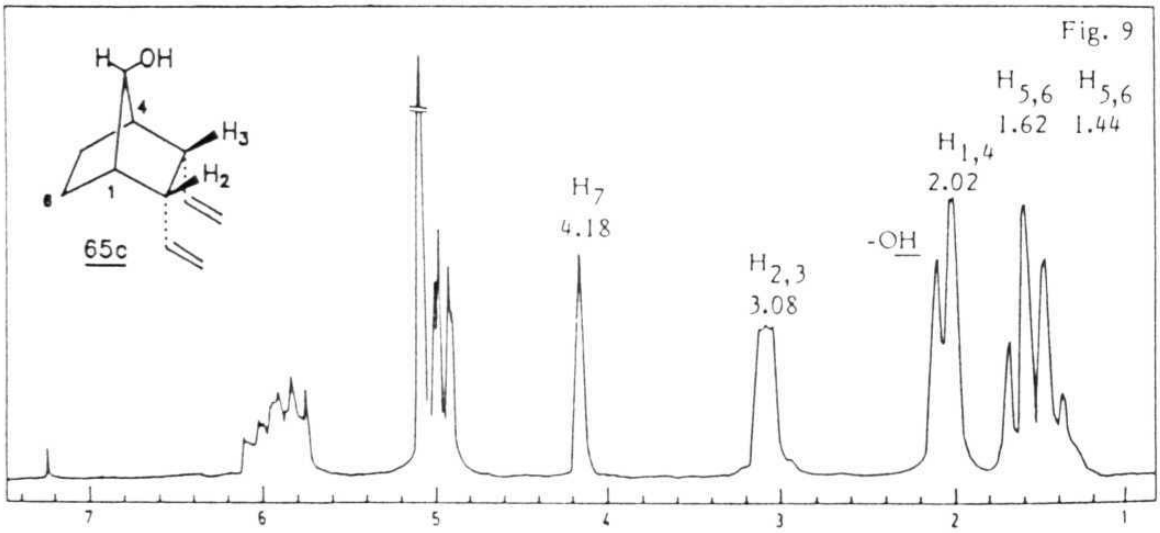


Fig. 9

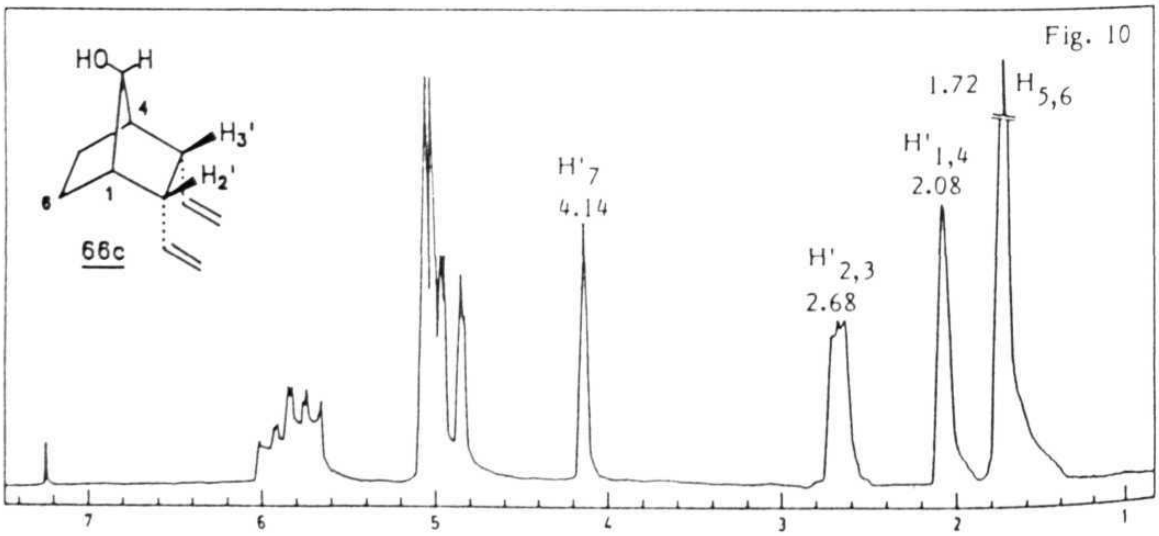


Fig. 10

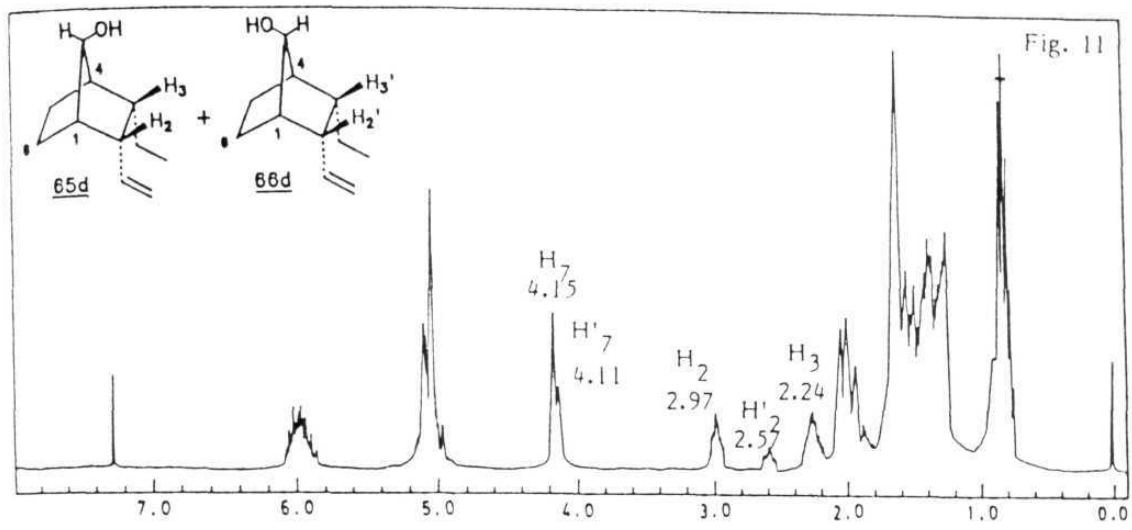


Fig. 11

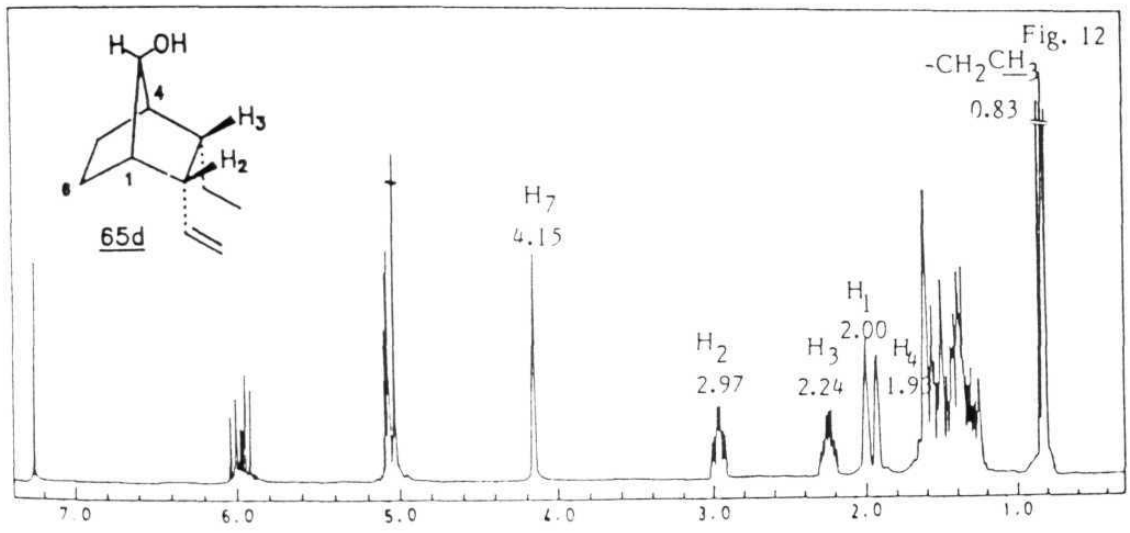


Fig. 12

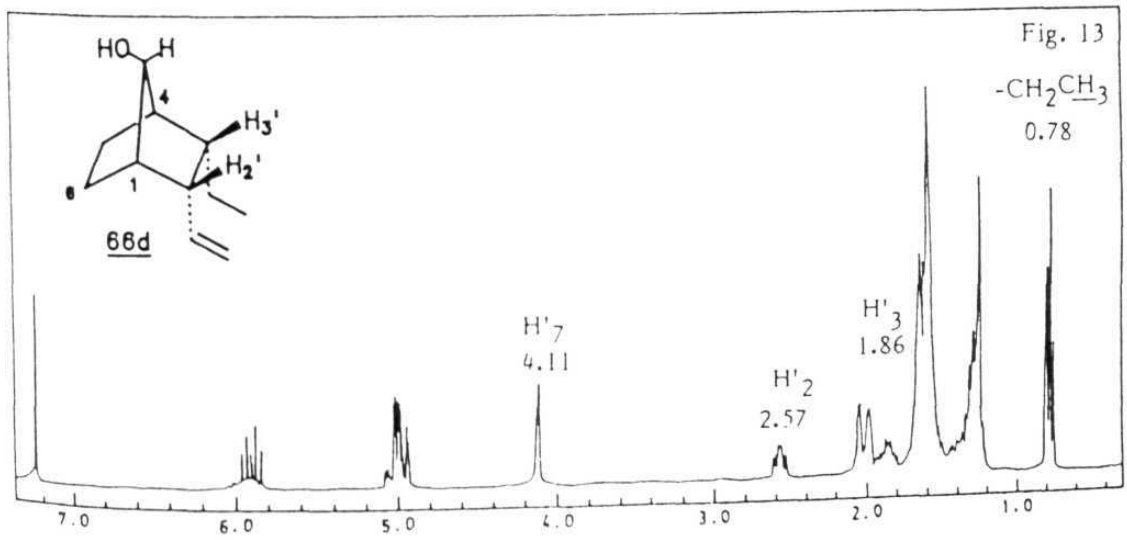


Fig. 13

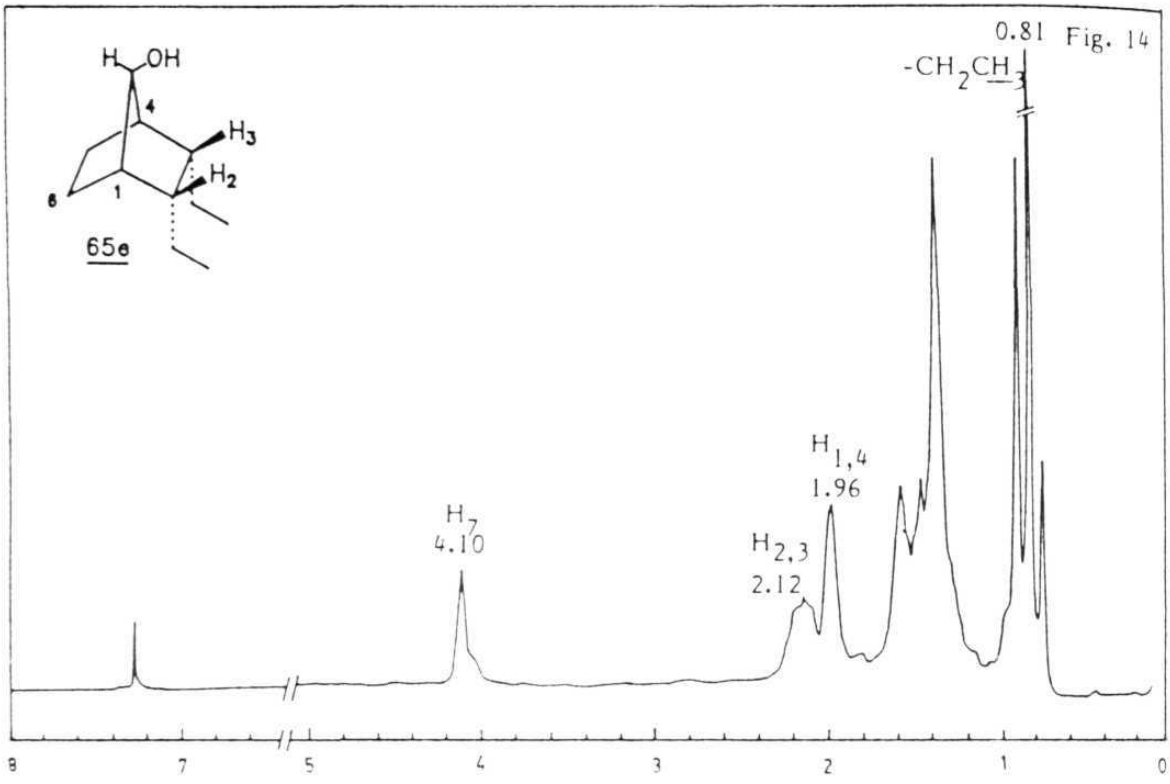

H OH
4
H3
H2
6
1
65e
0.81
-CH2CH3
H1,4
1.96
H7
4.10
H2,3
2.12
8
7
5
4
3
2
1
0

Fig. 14

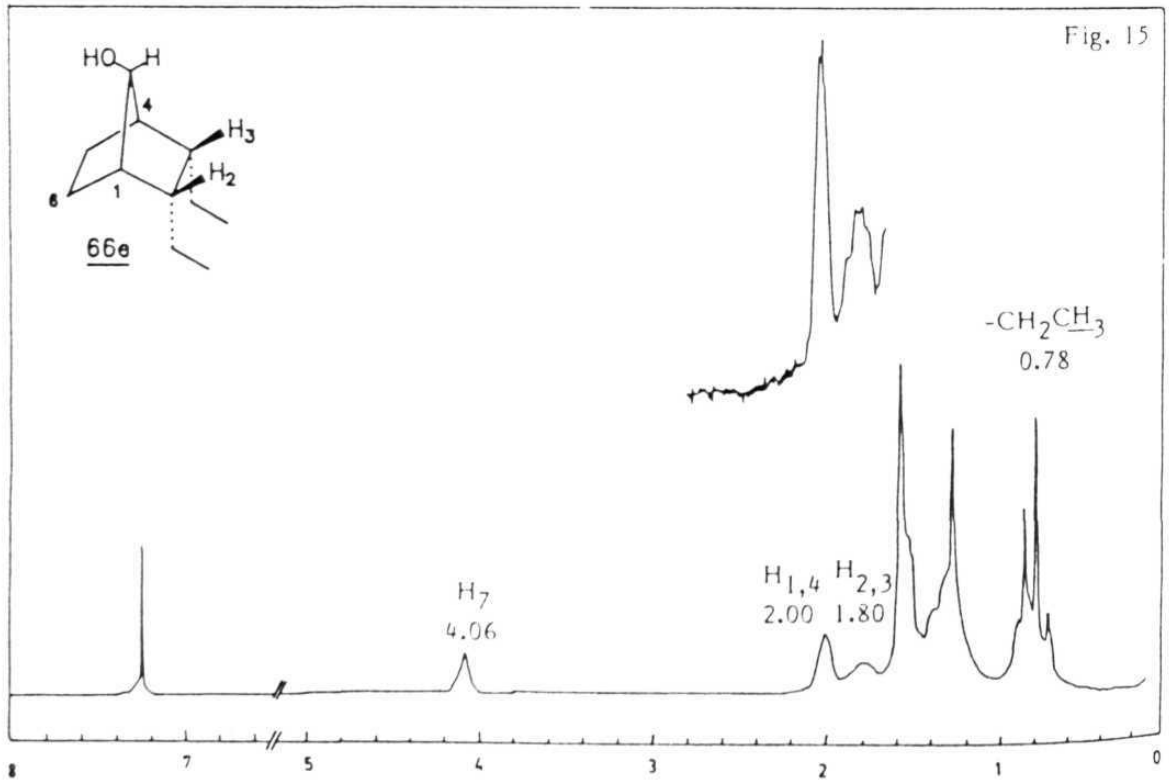

HO H
4
H3
H2
6
1
66e
-CH2CH3
0.78
H7
4.06
H1,4
2.00
H2,3
1.80
8
7
5
4
3
2
1
0

Fig. 15

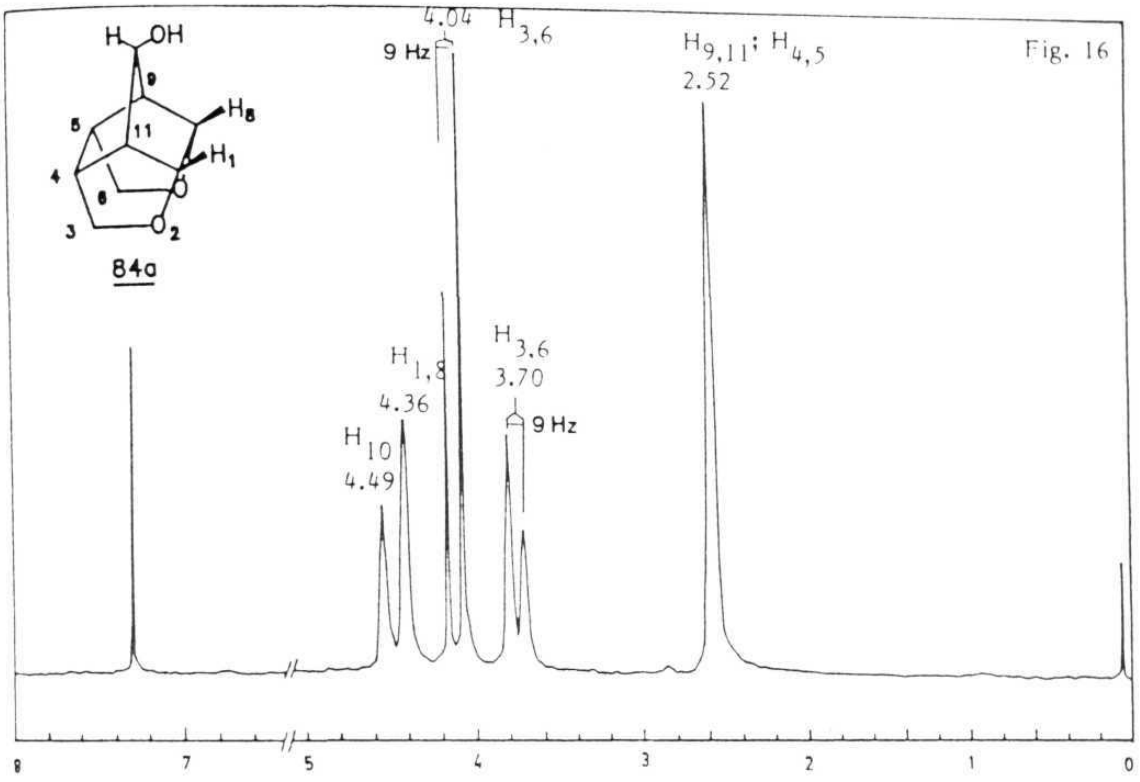

H OH
9
H8
5
11
H1
4
6
3
O2
84a
4.04 H3,6
9 Hz
H9,11; H4,5
2.52
H1,8
4.36
H10
4.49
H3,6
3.70
9 Hz
8
7
5
4
3
2
1
0

Fig. 16

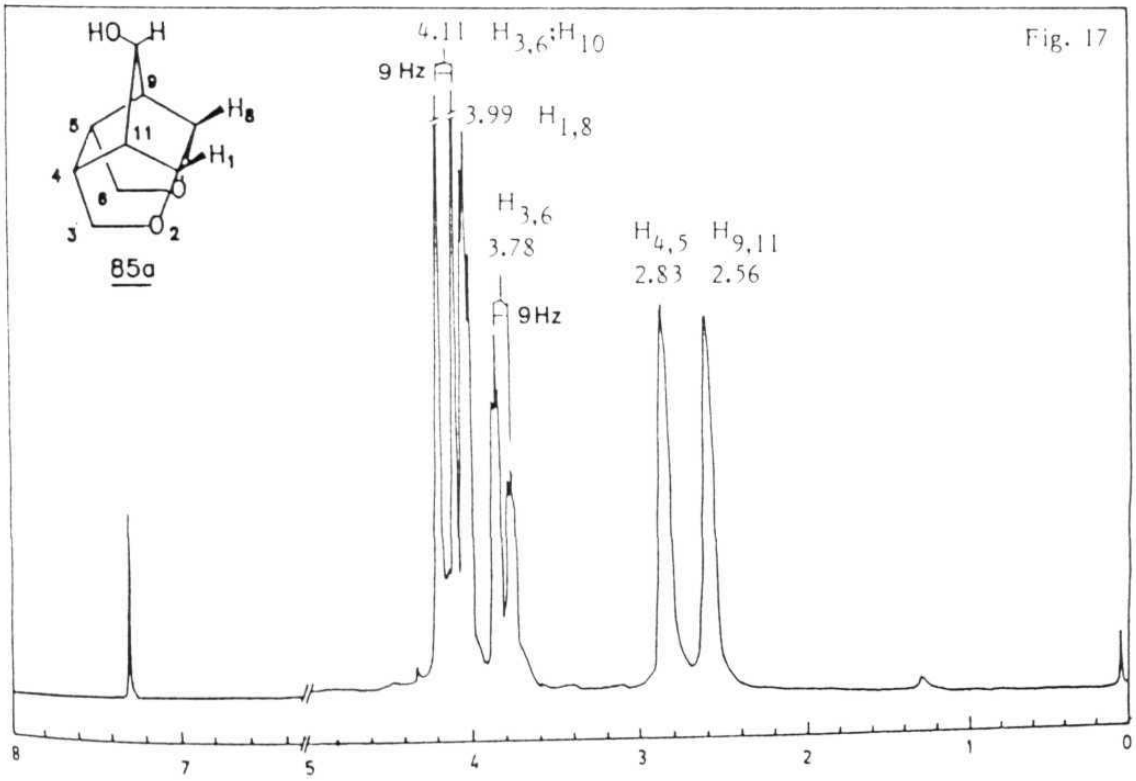

HO H
9
H8
5
11
H1
4
6
3
O2
85a
4.11 H3,6;H10
9 Hz
3.99 H1,8
H3,6
3.78
9Hz
H4,5 H9,11
2.83 2.56
8
7
5
4
3
2
1
0

Fig. 17

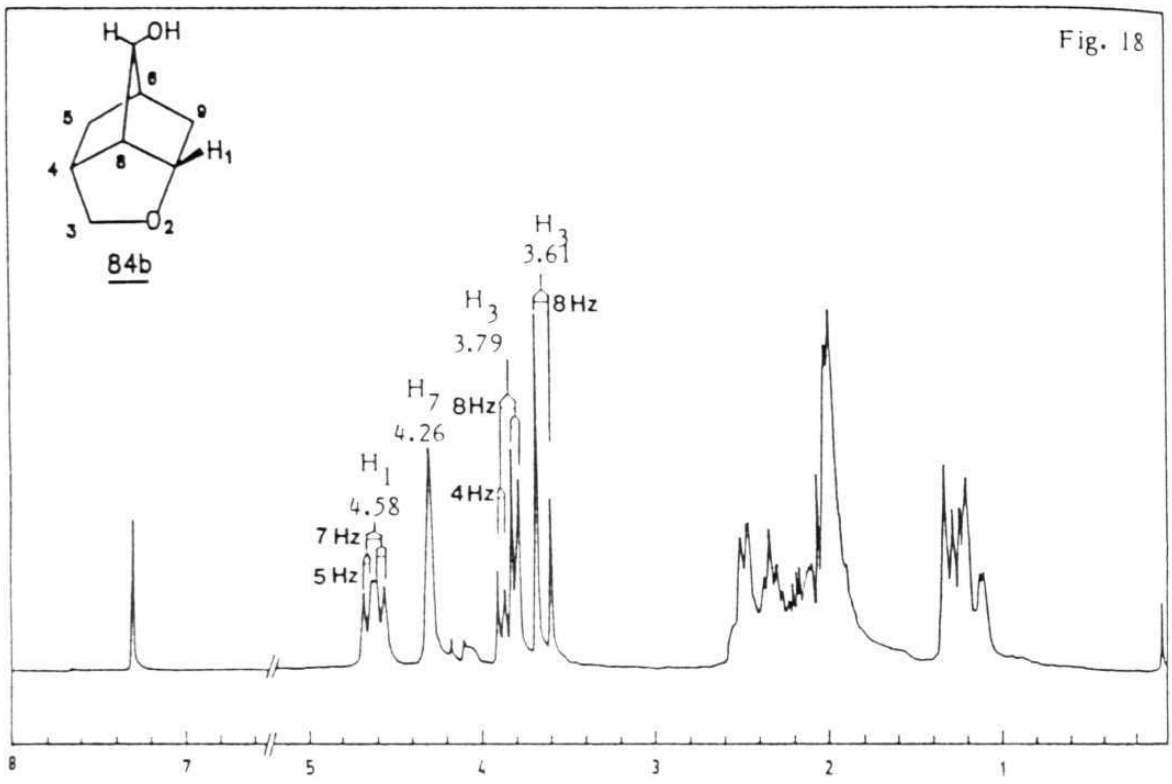

H OH
6
5
9
4
8
H1
3
O2
84b
H3
3.61
8Hz
H3
3.79
8Hz
H7
4.26
H1
4.58
4Hz
7 Hz
5 Hz
8
7
5
4
3
2
1

Fig. 18

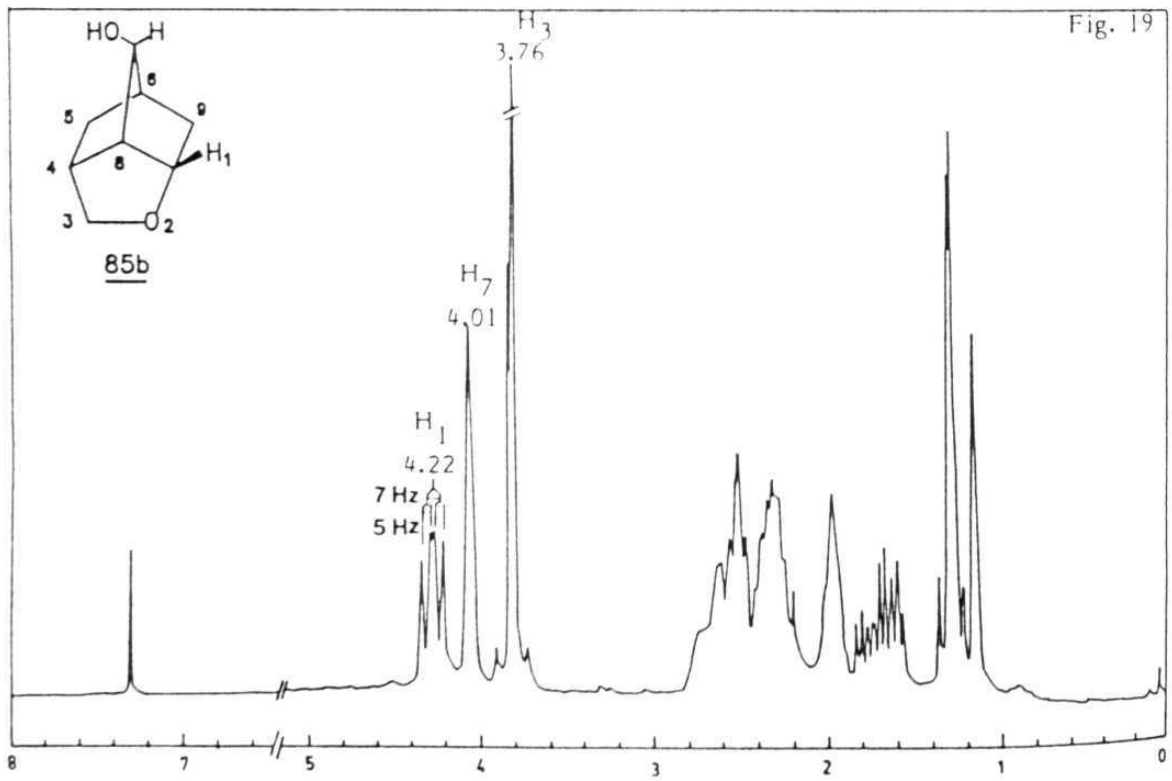

HO H
6
5
9
4
8
H1
3
O2
85b
H3
3.76
H7
4.01
H1
4.22
7 Hz
5 Hz
8
7
5
4
3
2
1
0

Fig. 19

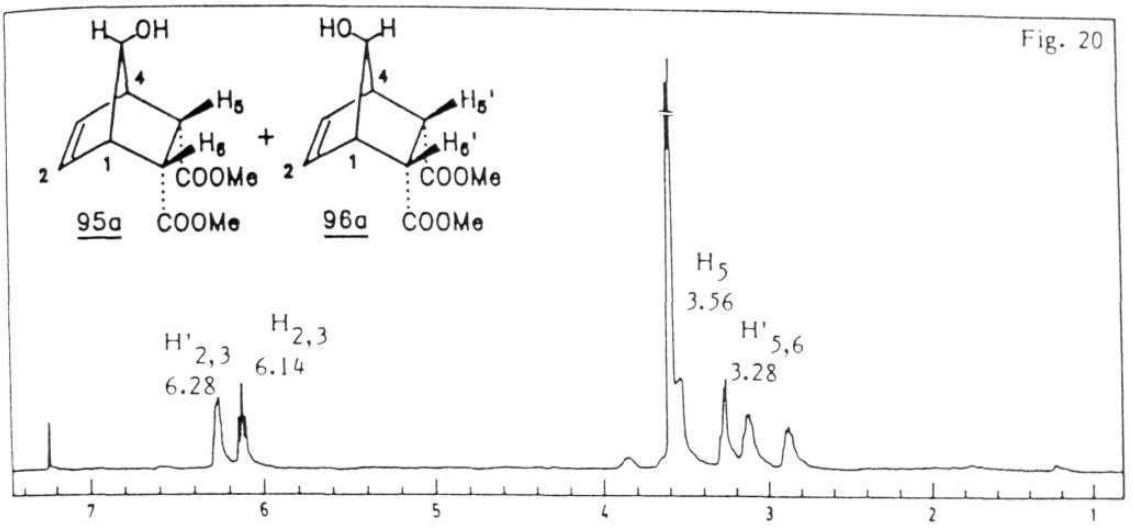


Fig. 20

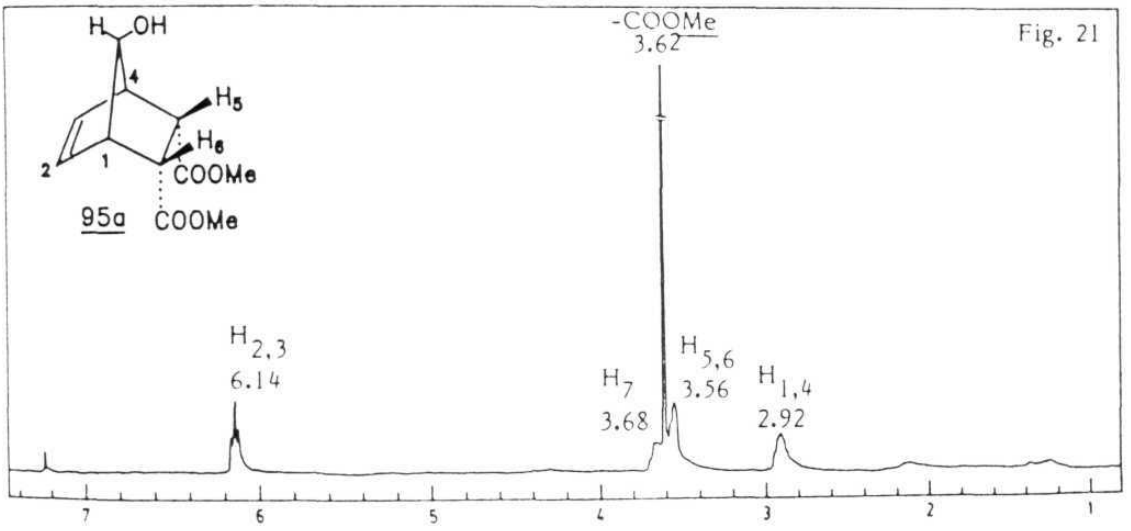


Fig. 21

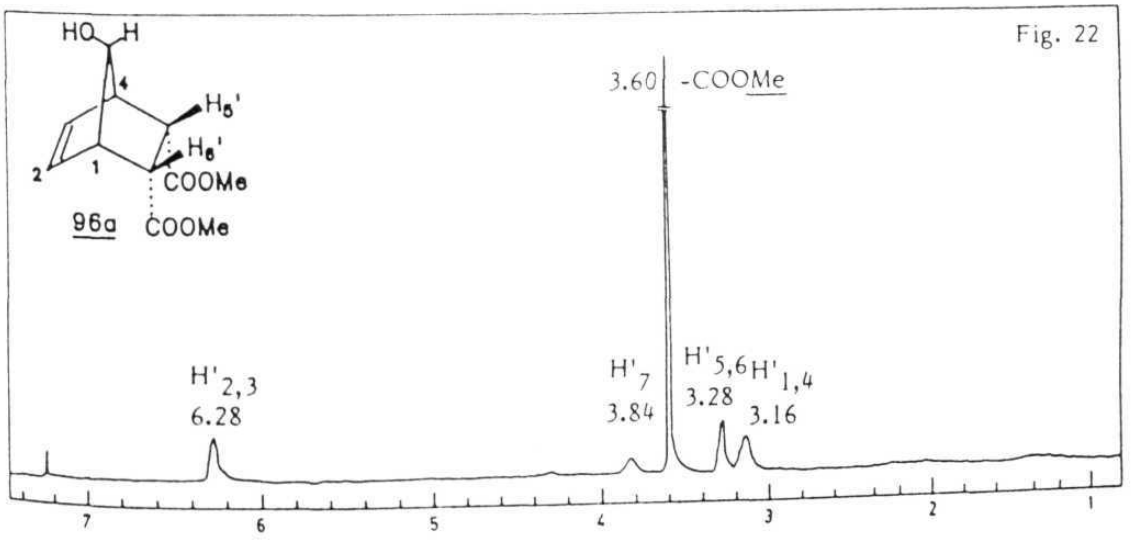
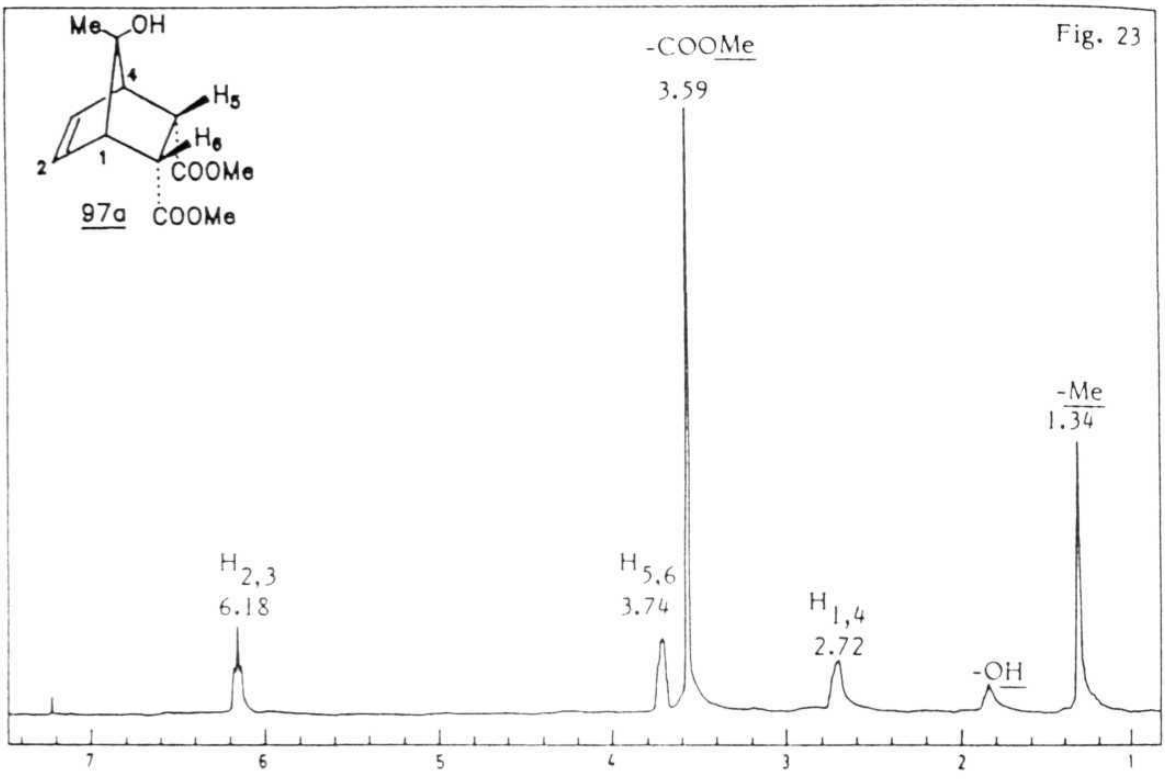


Fig. 22


Me
OH
4
H5
H6
2
1
COOMe
97a
COOMe
-COOMe
3.59
Fig. 23
-Me
1.34
H2,3
6.18
H5,6
3.74
H1,4
2.72
-OH
7
6
5
4
3
2
1

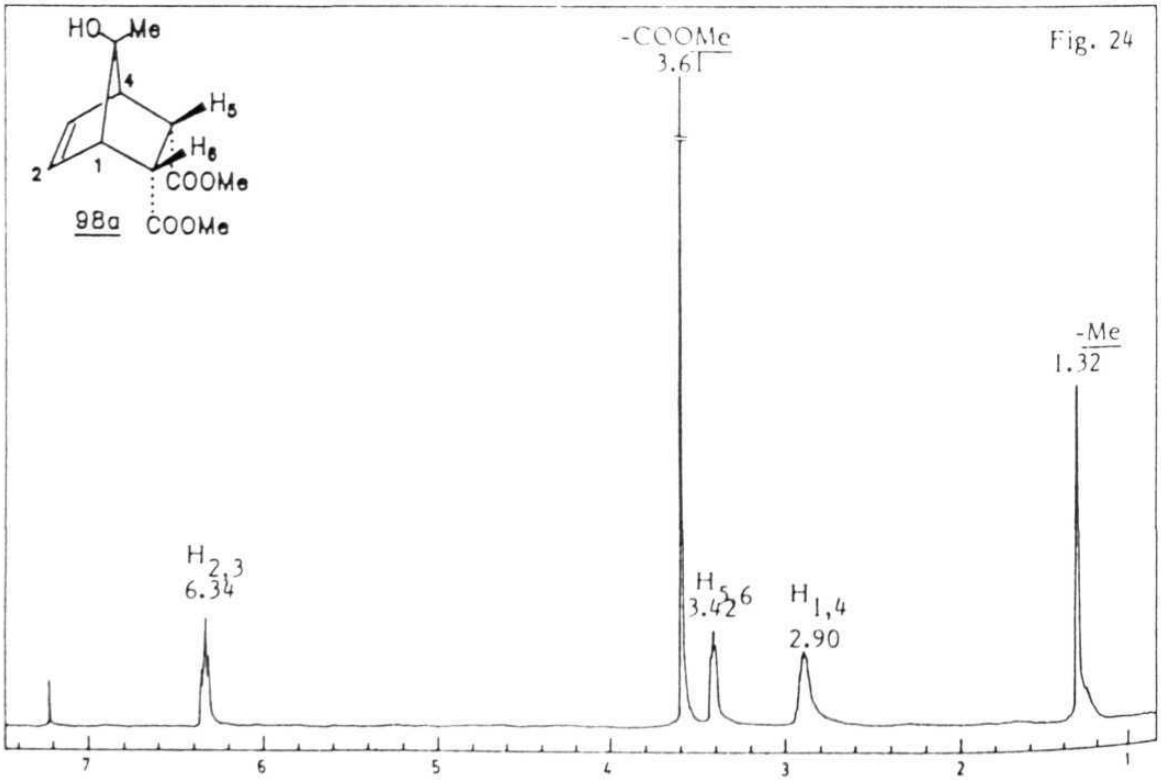

HO
Me
4
H5
H6
2
1
COOMe
98a
COOMe
-COOMe
3.61
Fig. 24
-Me
1.32
H2,3
6.34
H5,6
3.42
H1,4
2.90
7
6
5
4
3
2
1

Fig. 25

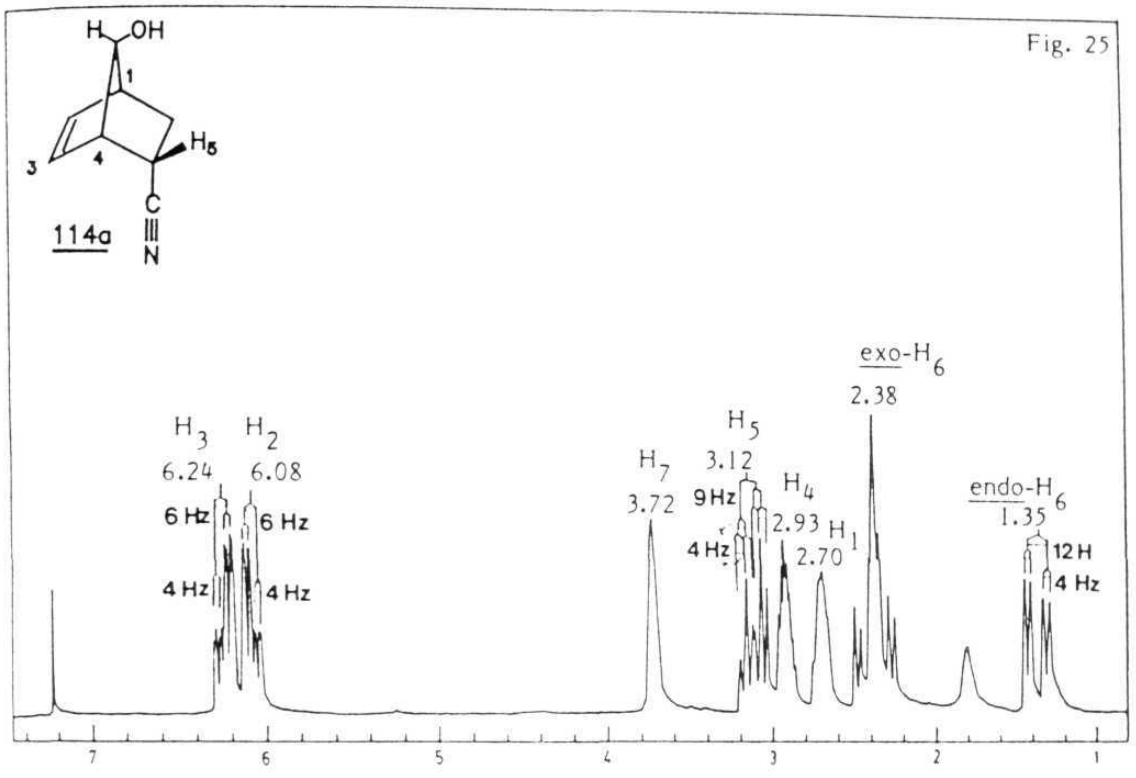
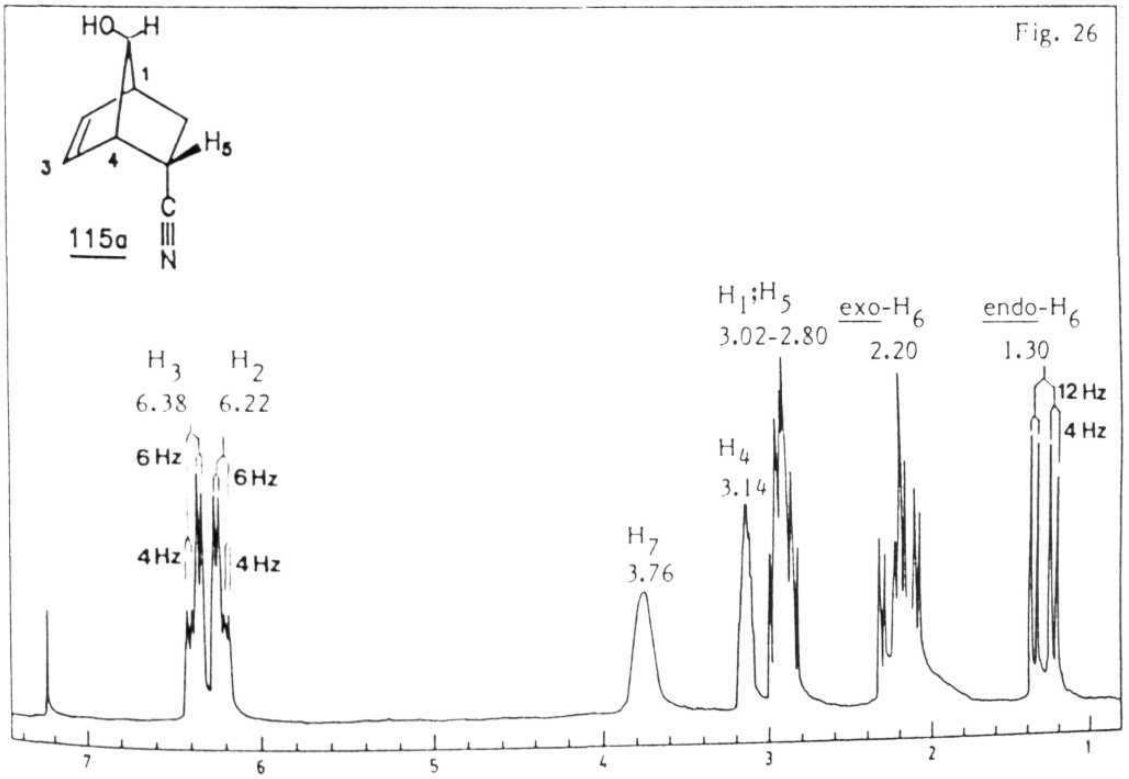

H OH
1
3
4
H5
C
N
114a
exo-H6
2.38
H3
6.24
H2
6.08
6 Hz
6 Hz
4 Hz
4 Hz
H7
3.72
H5
3.12
9Hz
4 Hz
H4
2.93
H1
2.70
endo-H6
1.35
12 H
4 Hz
7
6
5
4
3
2
1

Fig. 26


HO H
1
3
4
H5
C
N
115a
H1;H5
3.02-2.80
exo-H6
2.20
endo-H6
1.30
12 Hz
4 Hz
H3
6.38
H2
6.22
6 Hz
6 Hz
4 Hz
4 Hz
H4
3.14
H7
3.76
7
6
5
4
3
2
1

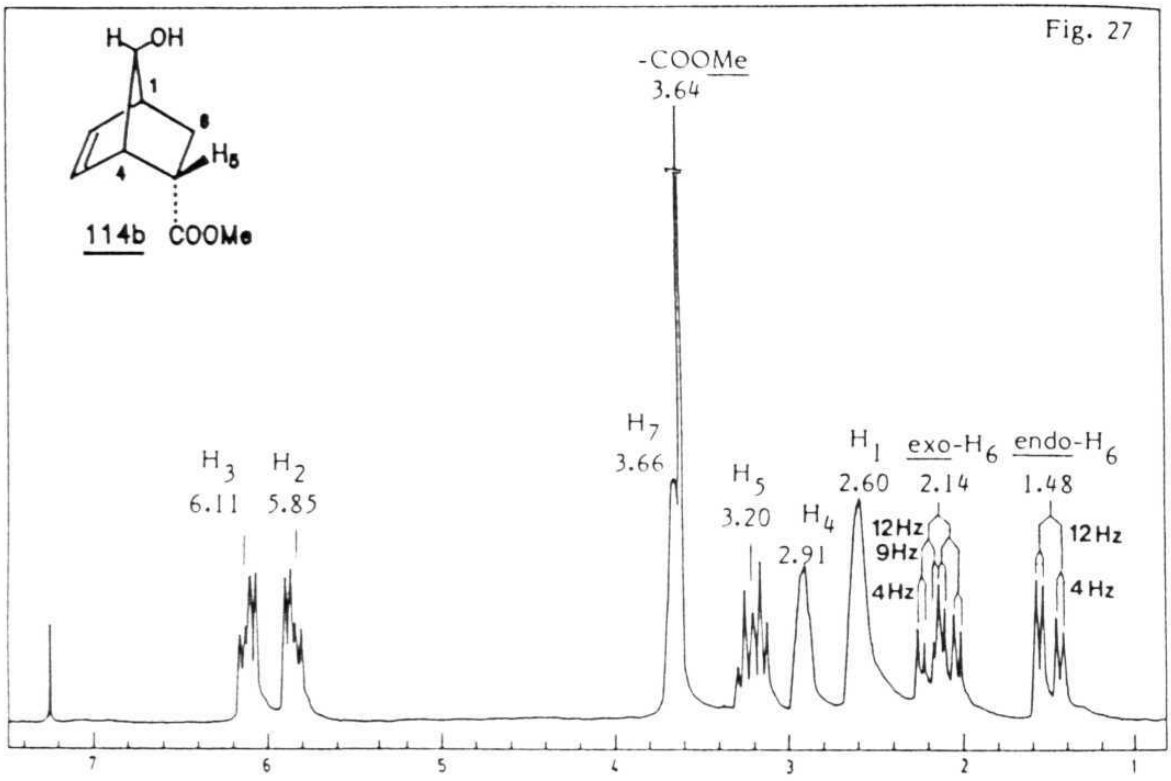

H OH
1
6
H5
4
114b COOMe
-COOMe
3.64
H7
3.66
H3 H2
6.11 5.85
H5
3.20
H4
2.91
H1 exo-H6 endo-H6
2.60 2.14 1.48
12Hz
9Hz
4Hz
12Hz
4Hz
7
6
5
4
3
2
1

Fig. 27

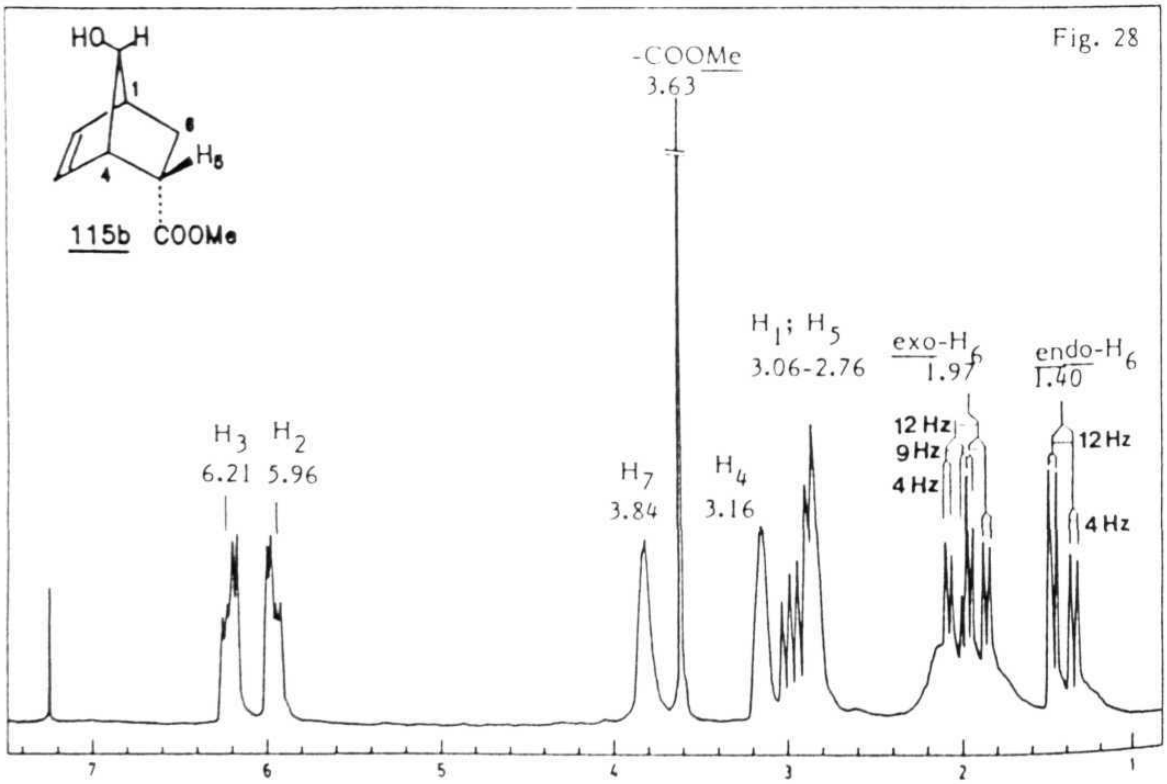

HO H
1
6
H5
4
115b COOMe
-COOMe
3.63
H1; H5
3.06-2.76
exo-H6
1.97
endo-H6
1.40
H3 H2
6.21 5.96
H7
3.84
H4
3.16
12 Hz
9 Hz
4 Hz
12Hz
4Hz
7
6
5
4
3
2
1

Fig. 28

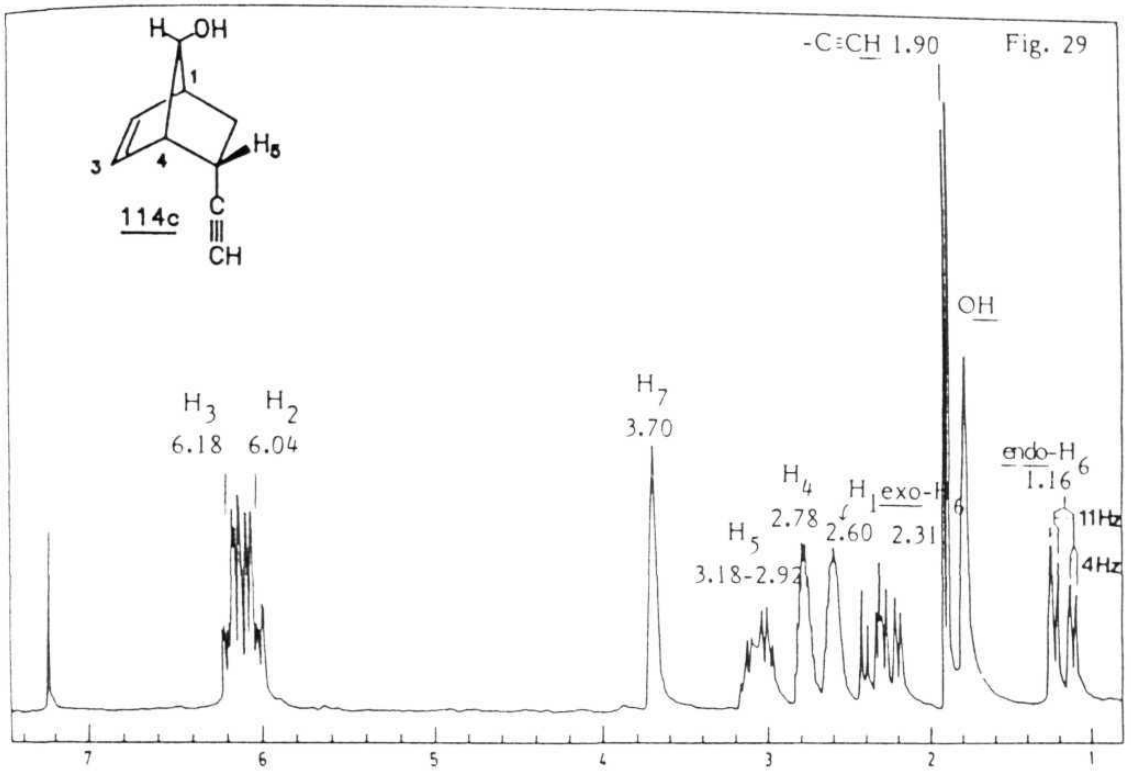

H OH
1
3
4
H5
C
CH
114c
-C≡CH 1.90
OH
H3 6.18
H2 6.04
H7 3.70
H4 2.78
H1 2.60
exo-H6 2.31
H5 3.18-2.93
endo-H6 1.16
11Hz
4Hz
7
6
5
4
3
2
1

Fig. 29

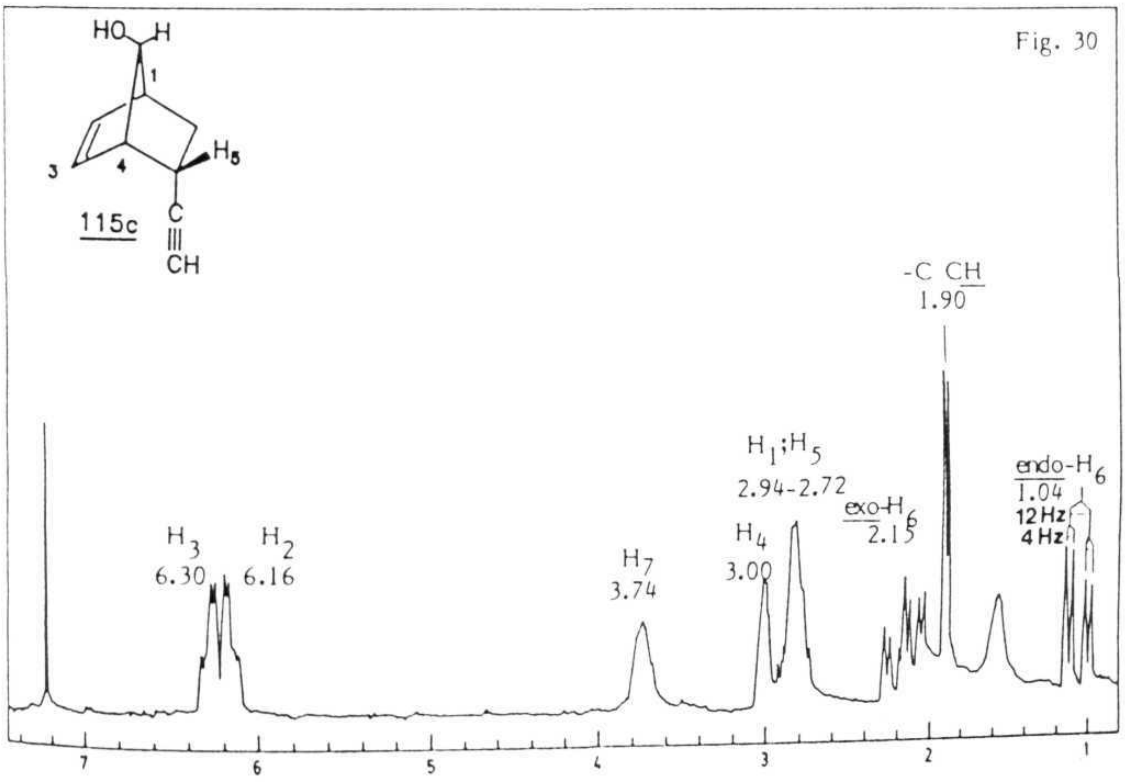

HO H
1
3
4
H5
C
CH
115c
-C CH 1.90
H1;H5 2.94-2.72
exo-H6 2.15
H4 3.00
H7 3.74
H3 6.30
H2 6.16
endo-H6 1.04
12Hz
4Hz
7
6
5
4
3
2
1

Fig. 30

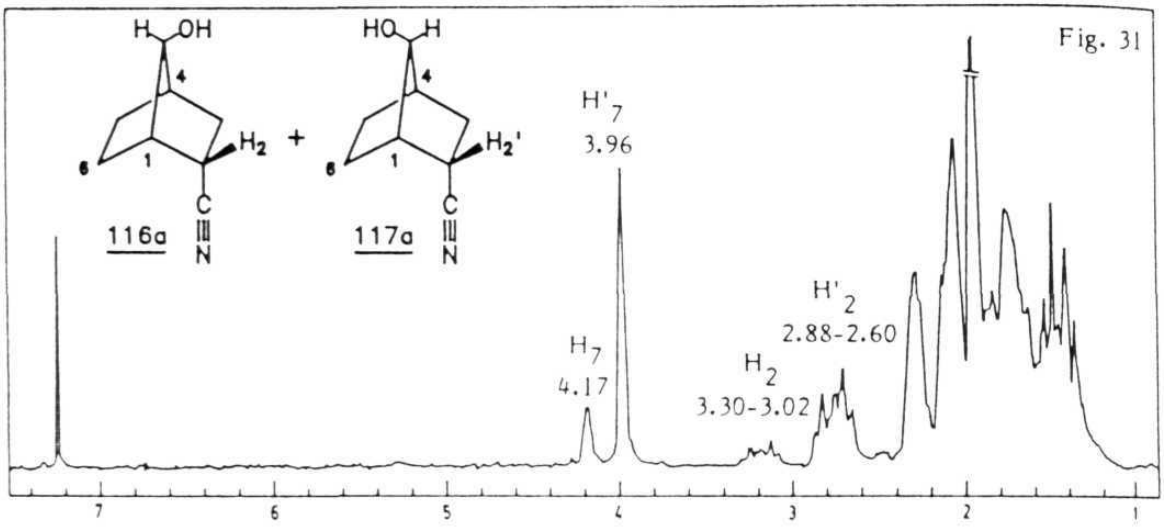


Fig. 31

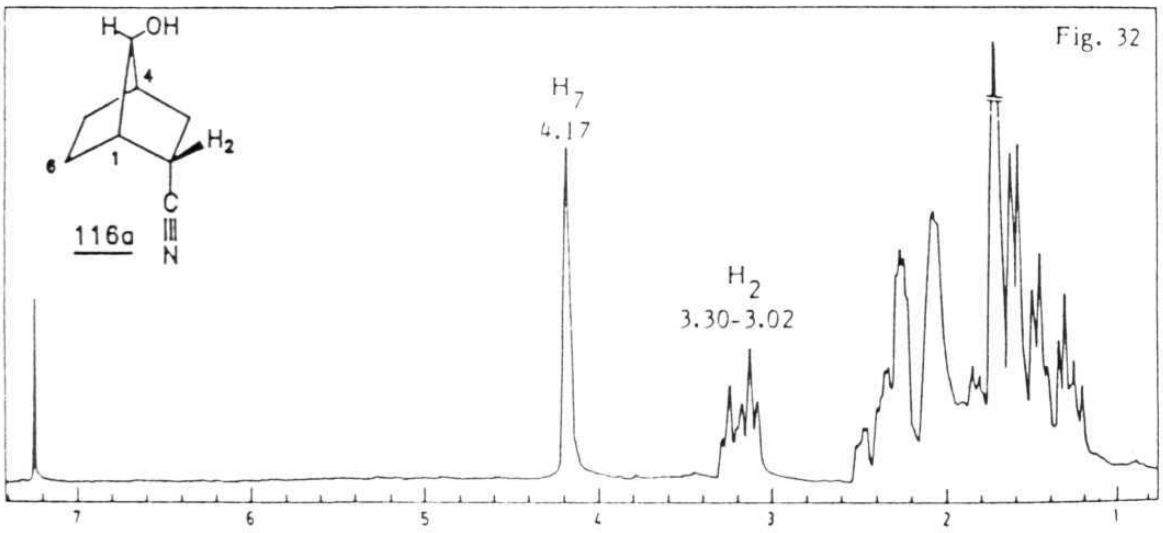


Fig. 32

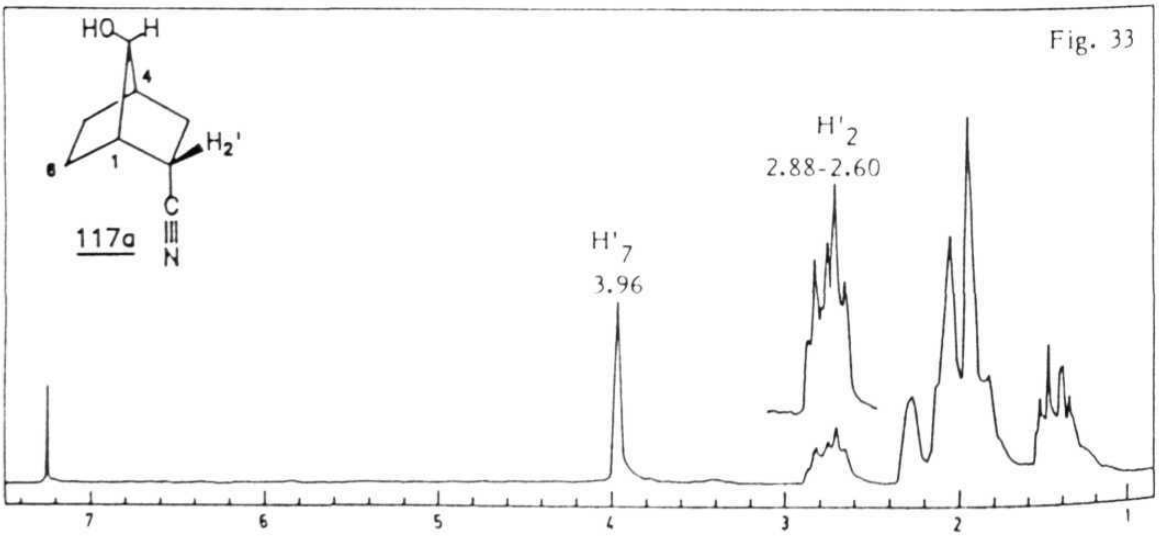


Fig. 33

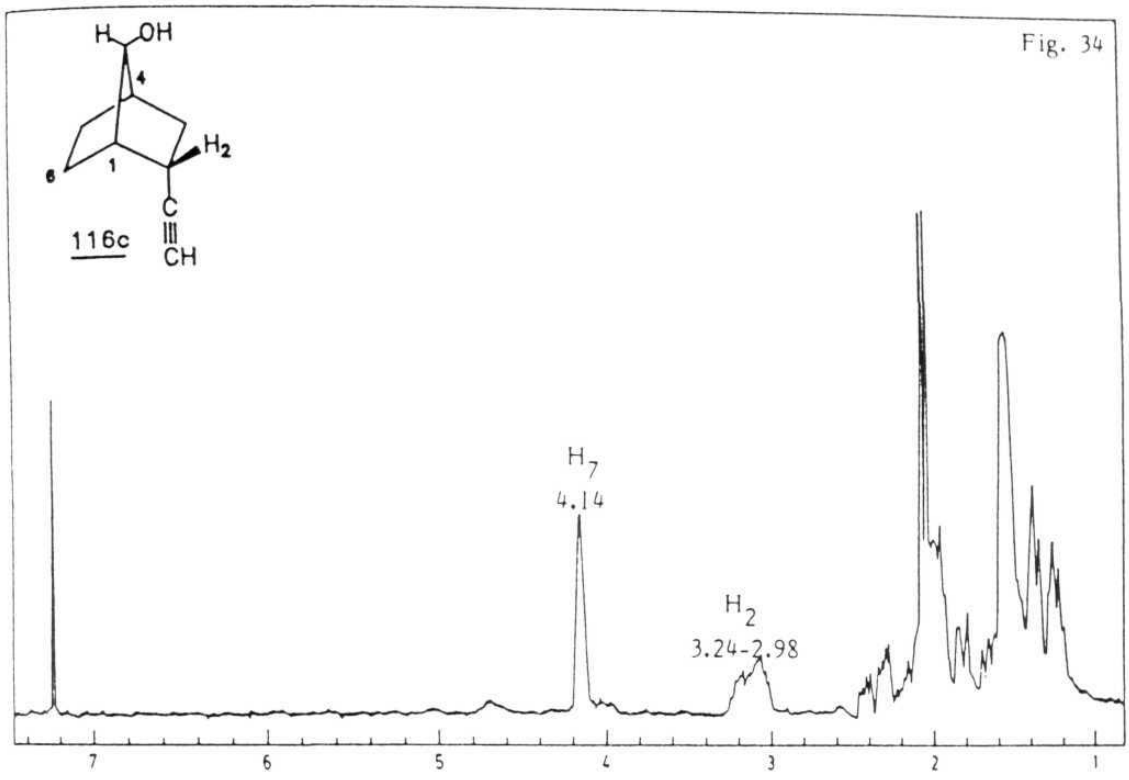

H OH
4
1
6
H2
C
III
CH
116c
H7
4.14
H2
3.24-2.98
7
6
5
4
3
2
1

Fig. 34

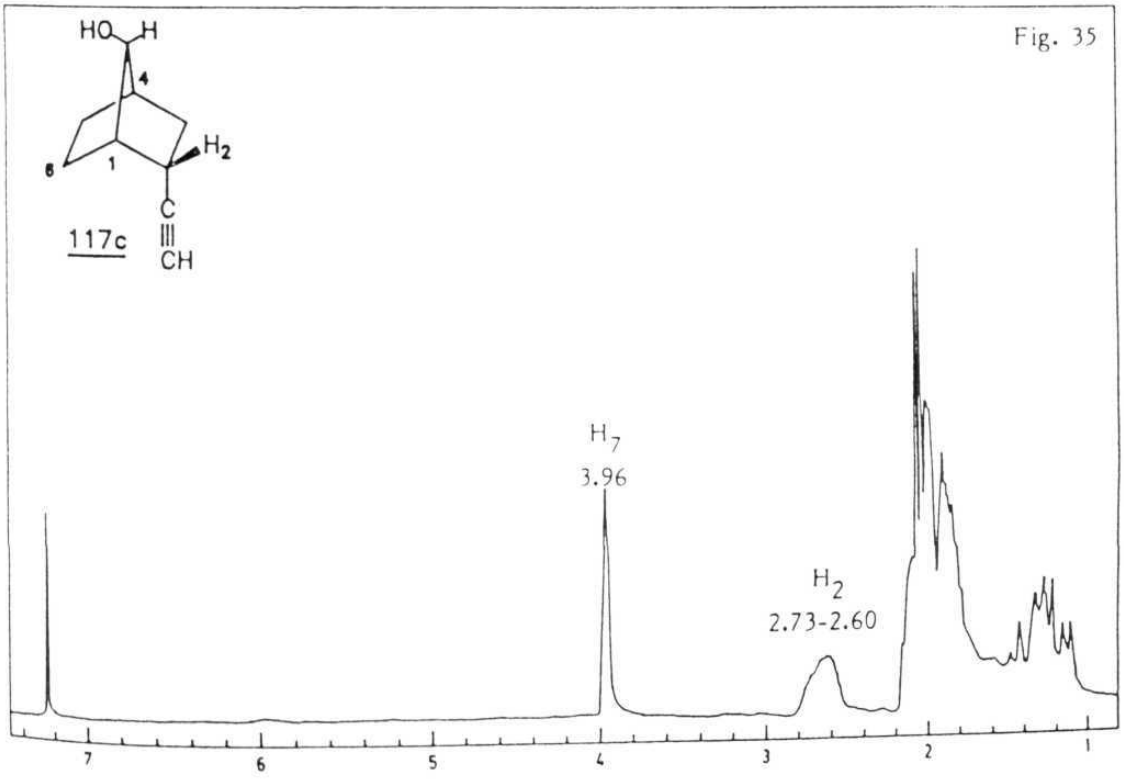

HO H
4
1
6
H2
C
III
CH
117c
H7
3.96
H2
2.73-2.60
7
6
5
4
3
2
1

Fig. 35

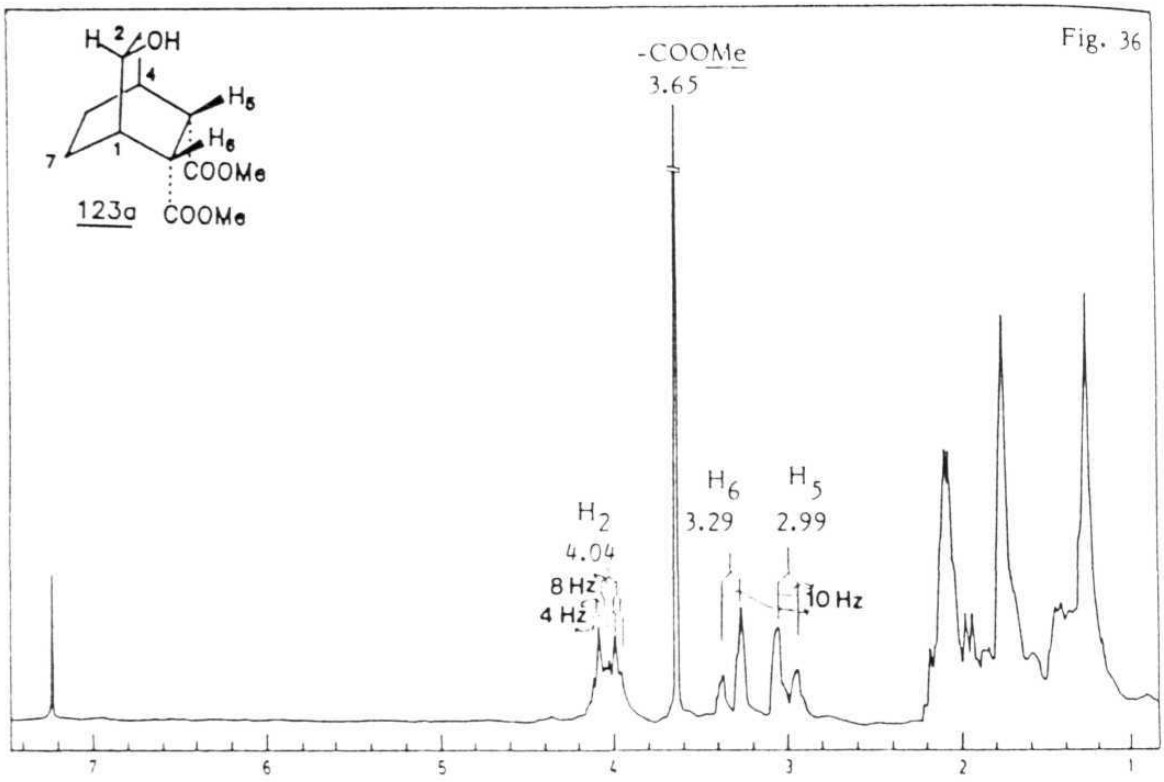

H 2 OH
4
H5
H6
7
1
COOMe
123a COOMe
-COOMe
3.65
H2
4.04
8 Hz
4 Hz
H6
3.29
H5
2.99
10 Hz
7
6
5
4
3
2
1

Fig. 36

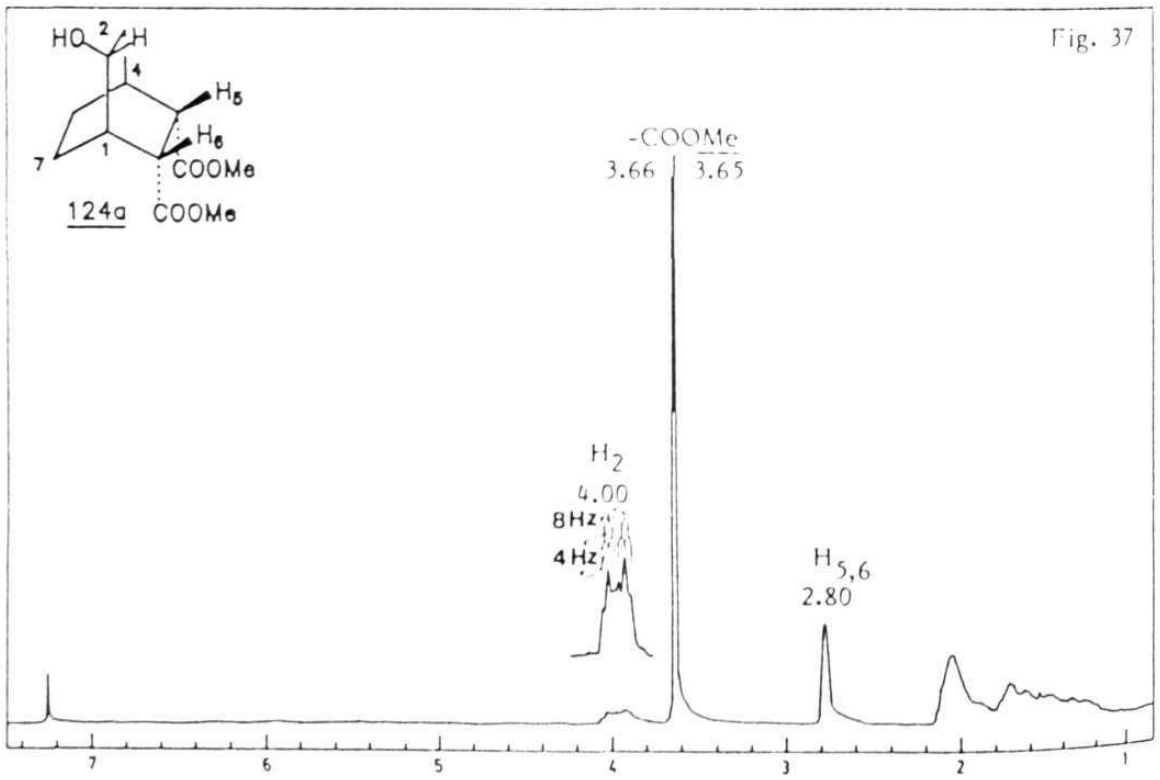
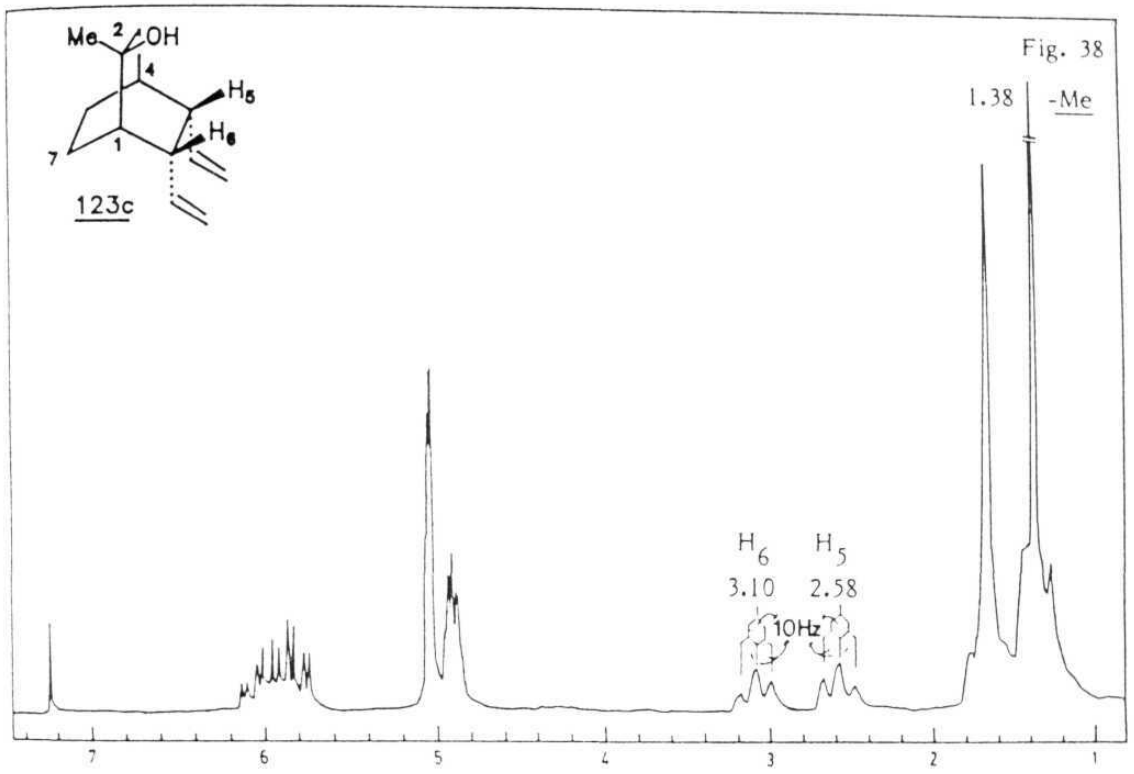
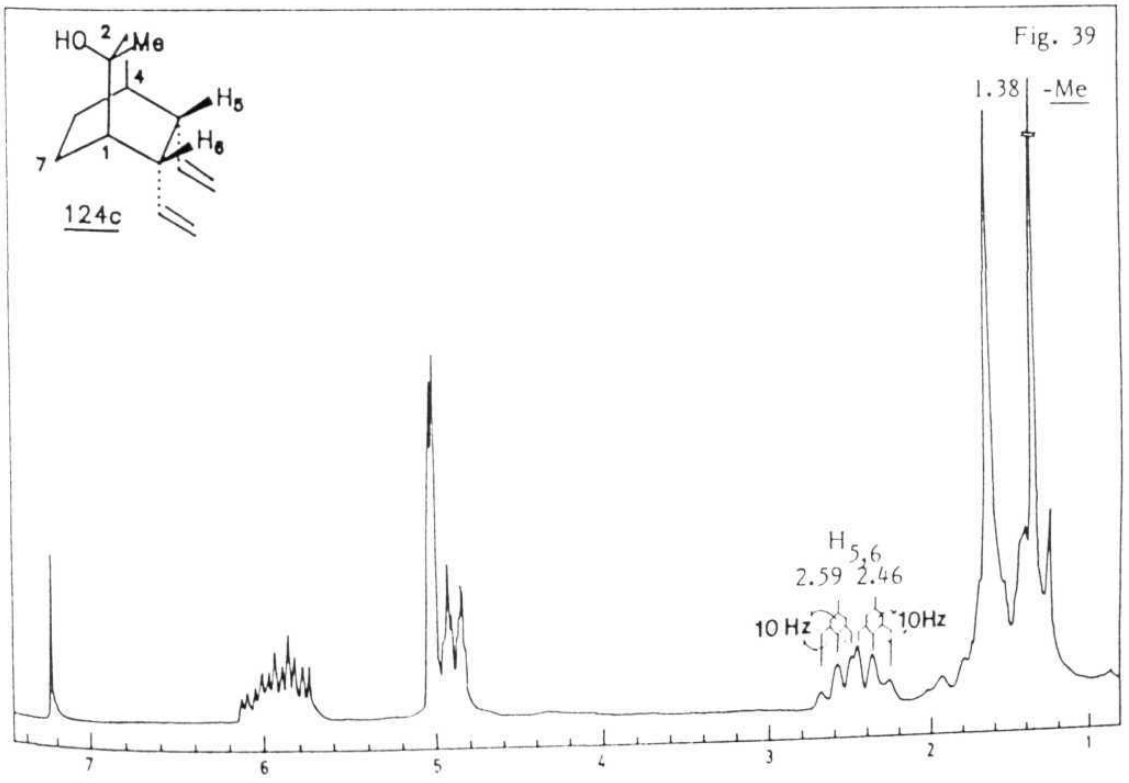

HO 2 H
4
H5
H6
7
1
COOMe
124a COOMe
-COOMe
3.66
3.65
H2
4.00
8Hz
4Hz
H5,6
2.80
7
6
5
4
3
2
1

Fig. 37


Me
2
OH
4
H5
H6
7
1
123c
Fig. 38
1.38
-Me
H6
3.10
H5
2.58
10Hz
7
6
5
4
3
2
1


HO
2
Me
4
H5
H6
7
1
124c
Fig. 39
1.38
-Me
H5,6
2.59
2.46
10 Hz
10Hz
7
6
5
4
3
2
1

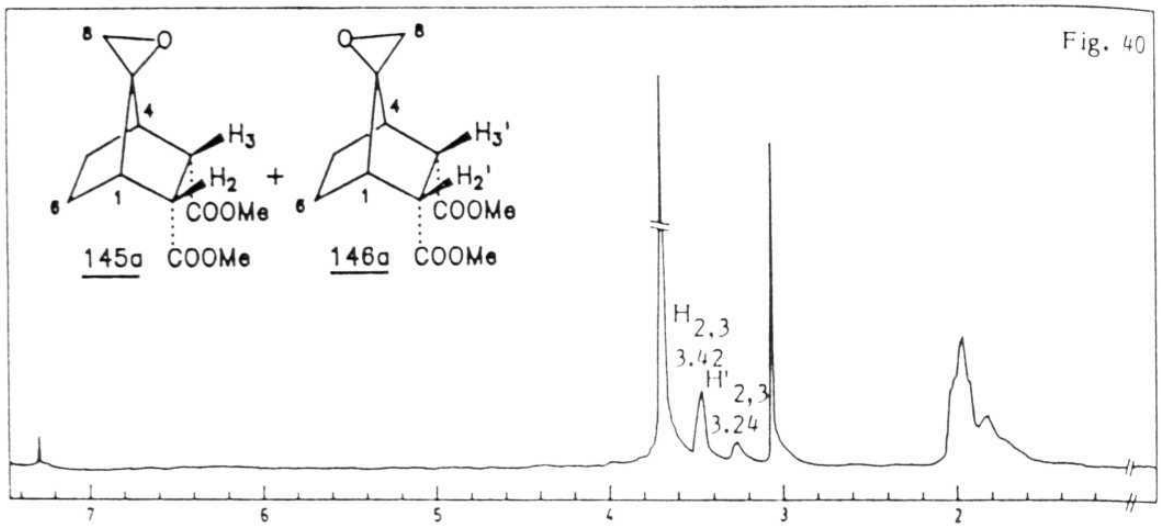


Fig. 40
145a COOMe
146a COOMe
H2,3
3.42
H'2,3
3.24

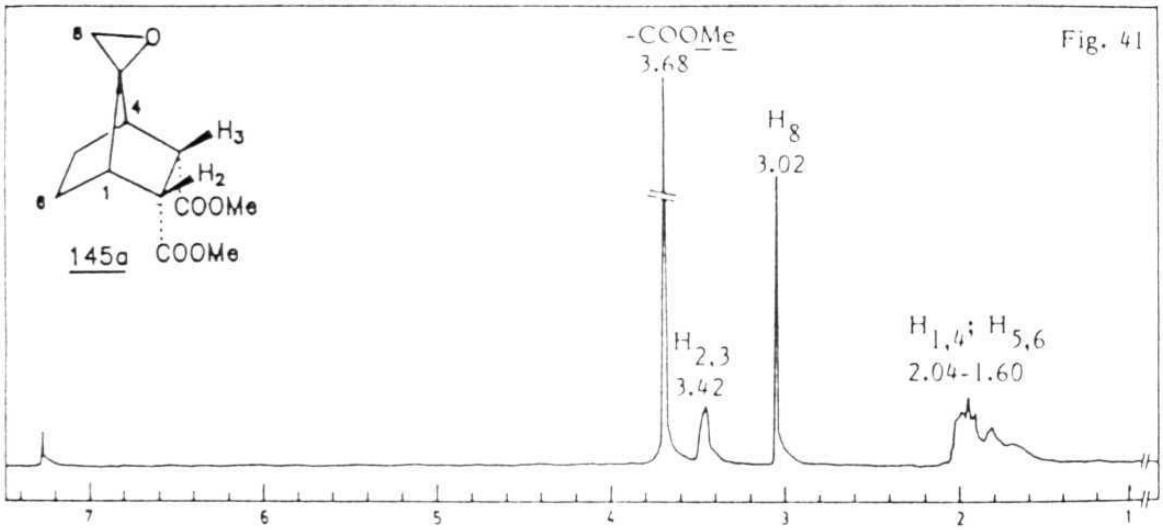


Fig. 41
-COOMe
3.68
H8
3.02
H2,3
3.42
H1,4; H5,6
2.04-1.60
145a COOMe

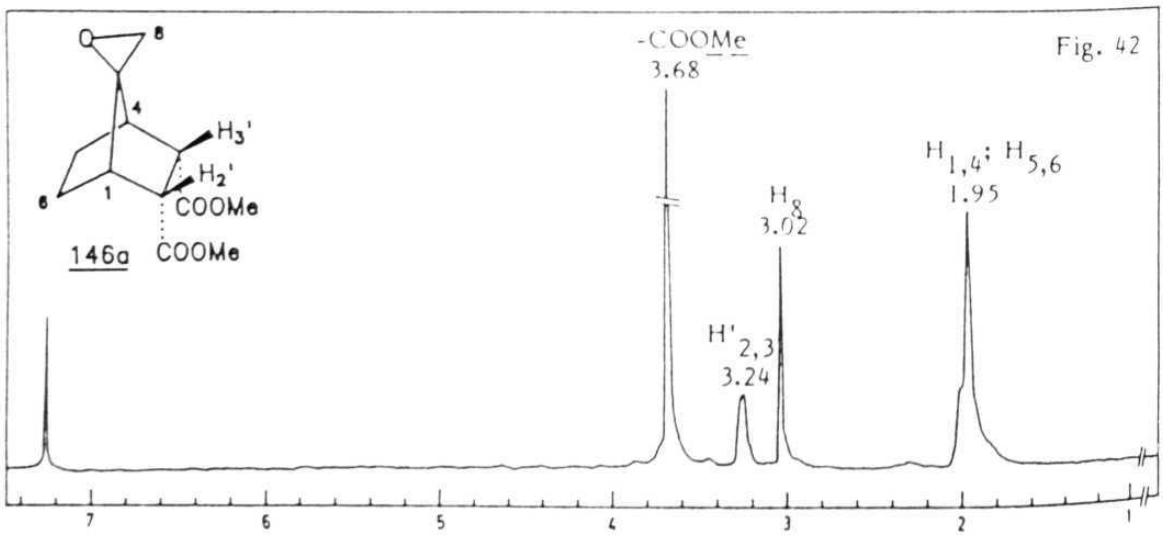


Fig. 42
-COOMe
3.68
H1,4; H5,6
1.95
H8
3.02
H'2,3
3.24
146a COOMe

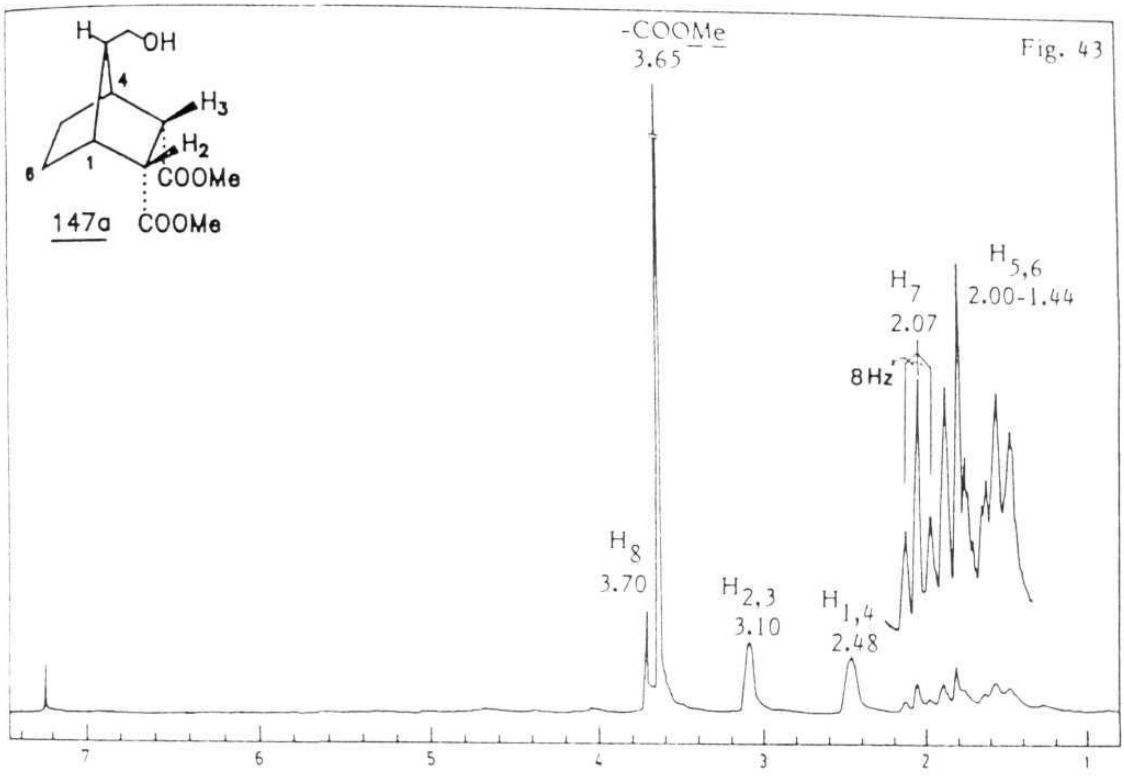

H
OH
4
H3
H2
6
1
COOMe
147a
COOMe
-COOMe
3.65
H5,6
2.00-1.44
H7
2.07
8Hz
H8
3.70
H2,3
3.10
H1,4
2.48
7
6
5
4
3
2
1

Fig. 43

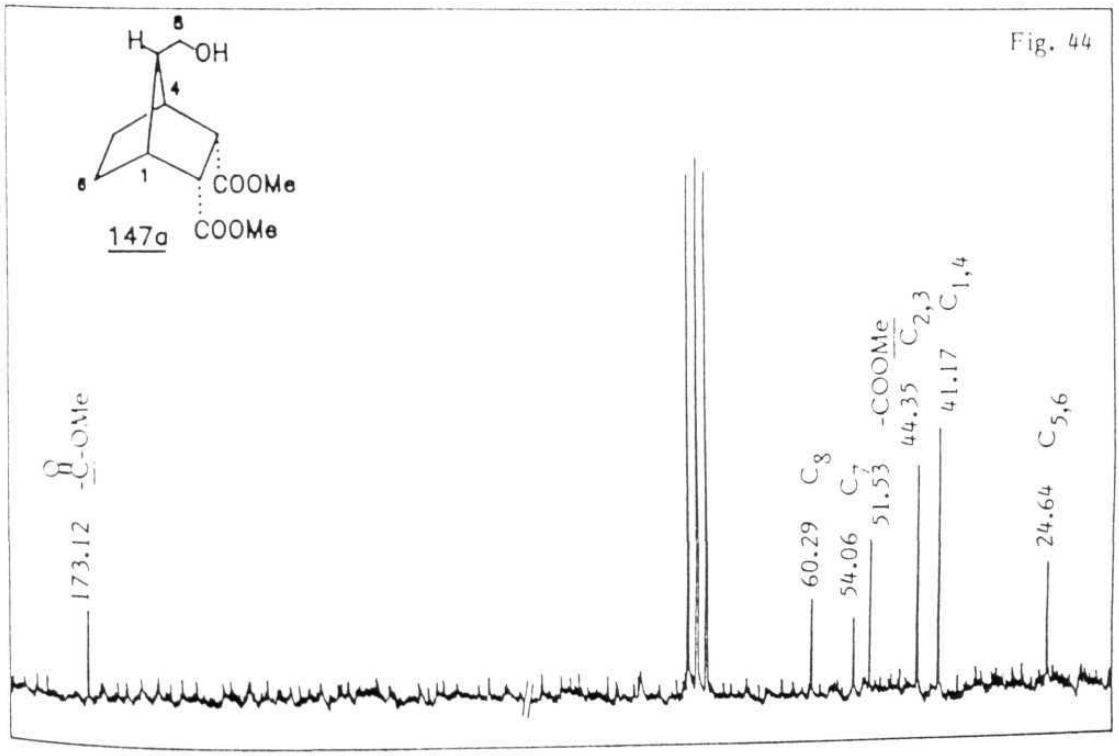
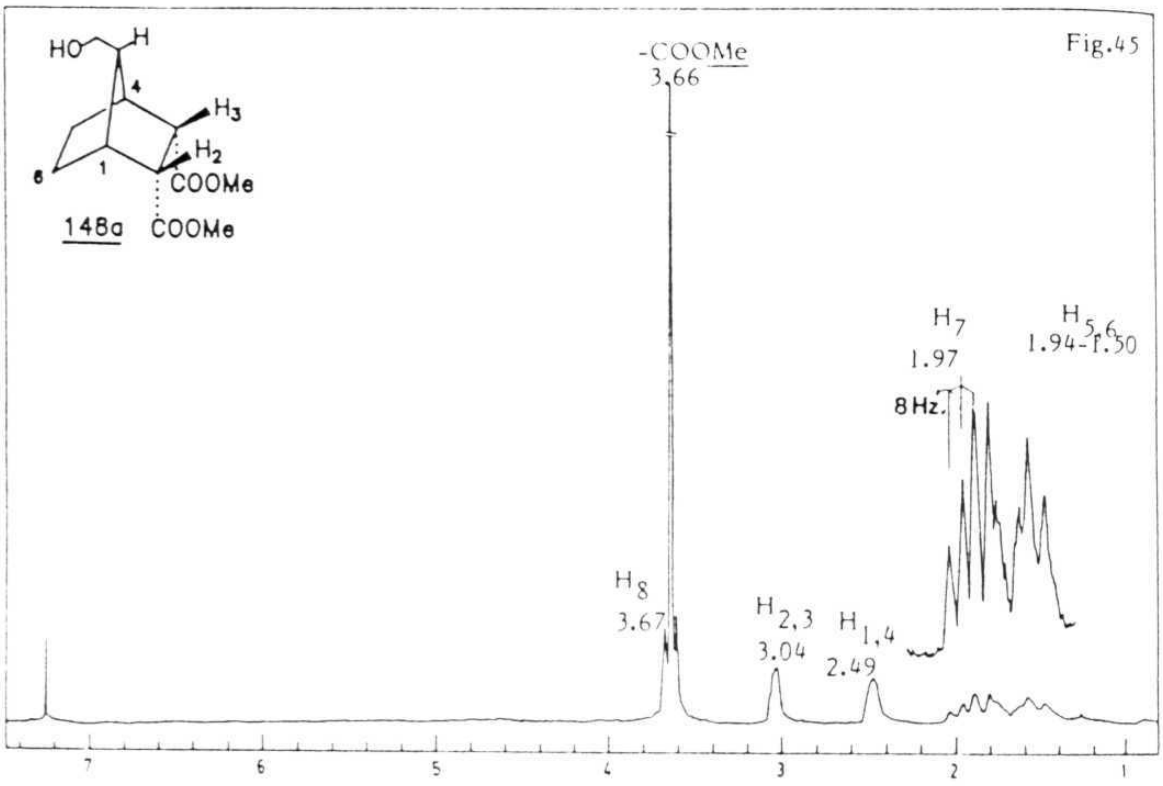
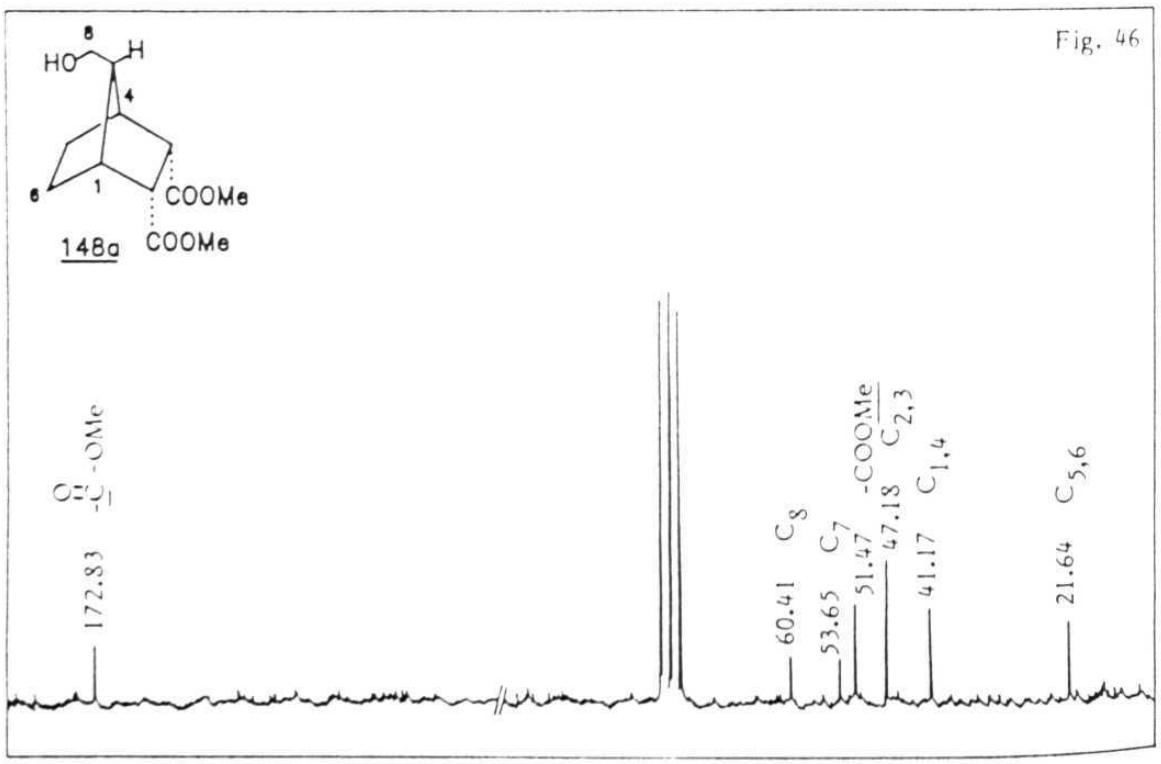
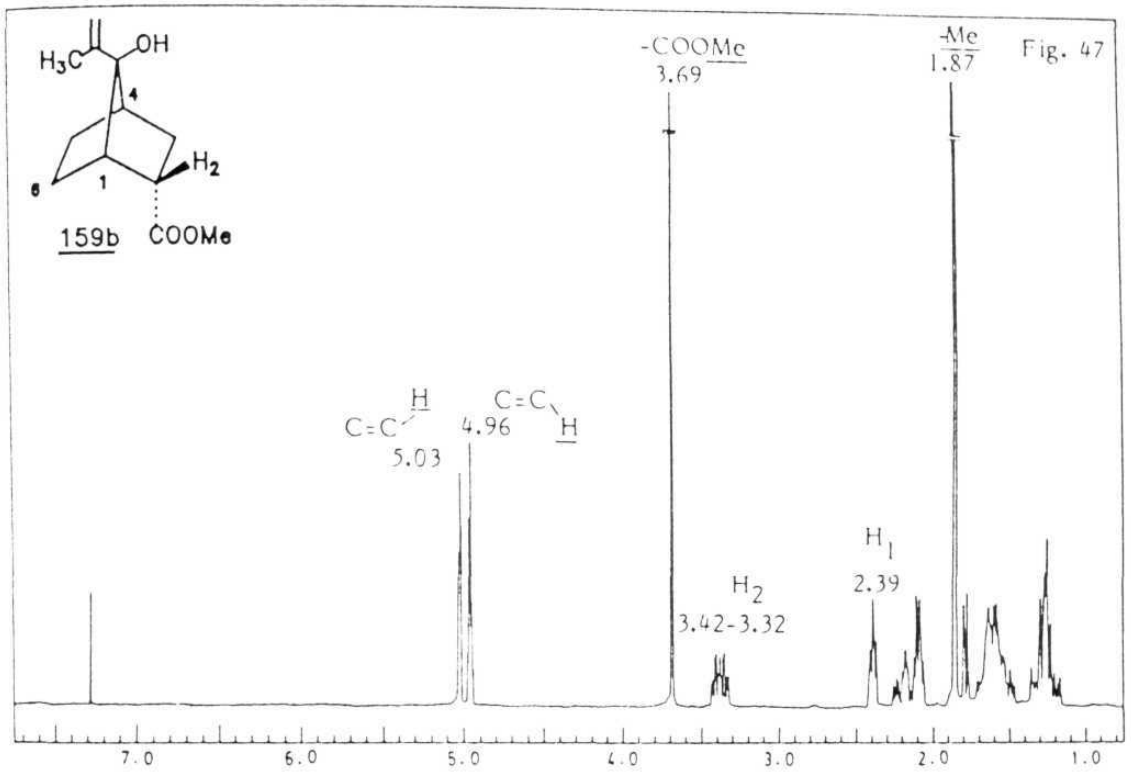

5
H
OH
4
6
1
COOMe
147a
COOMe
O
-C-OMe
173.12
C8
60.29
C7
54.06
51.53
-COOMe
C2,3
44.35
C1,4
41.17
C5,6
24.64

Fig. 44


HO
H
4
H3
H2
6
1
COOMe
148a
COOMe
-COOMe
3.66
H7
1.97
8 Hz.
H5,6
1.94-1.50
H8
3.67
H2,3
3.04
H1,4
2.49
7
6
5
4
3
2
1
Fig.45


HO
8
H
4
6
1
COOMe
148a
COOMe
O
-C-OMe
172.83
60.41 C8
53.65 C7
51.47
-COOMe
47.18 C2,3
41.17 C1,4
21.64 C5,6
Fig. 46


H3C
OH
4
6
1
H2
159b COOMe
-COOMe
3.69
-Me
1.87
Fig. 47
H
C=C
5.03
C=C
4.96
H
H2
3.42-3.32
H1
2.39
7.0
6.0
5.0
4.0
3.0
2.0
1.0

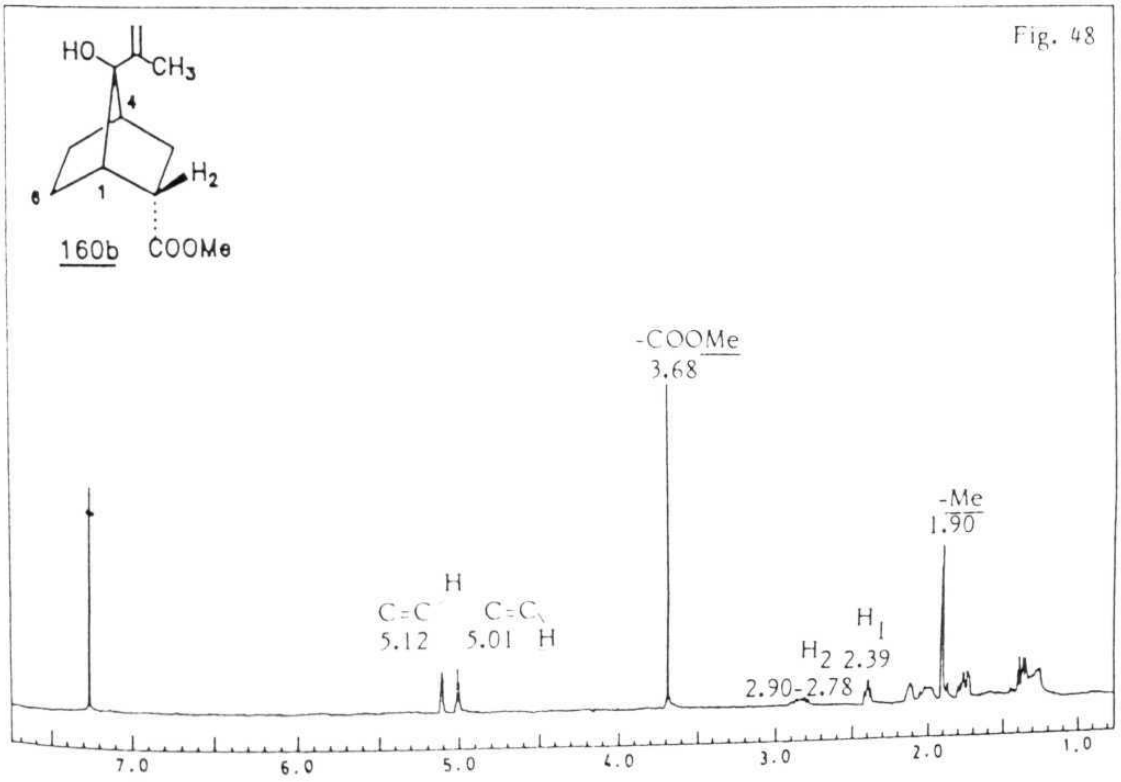
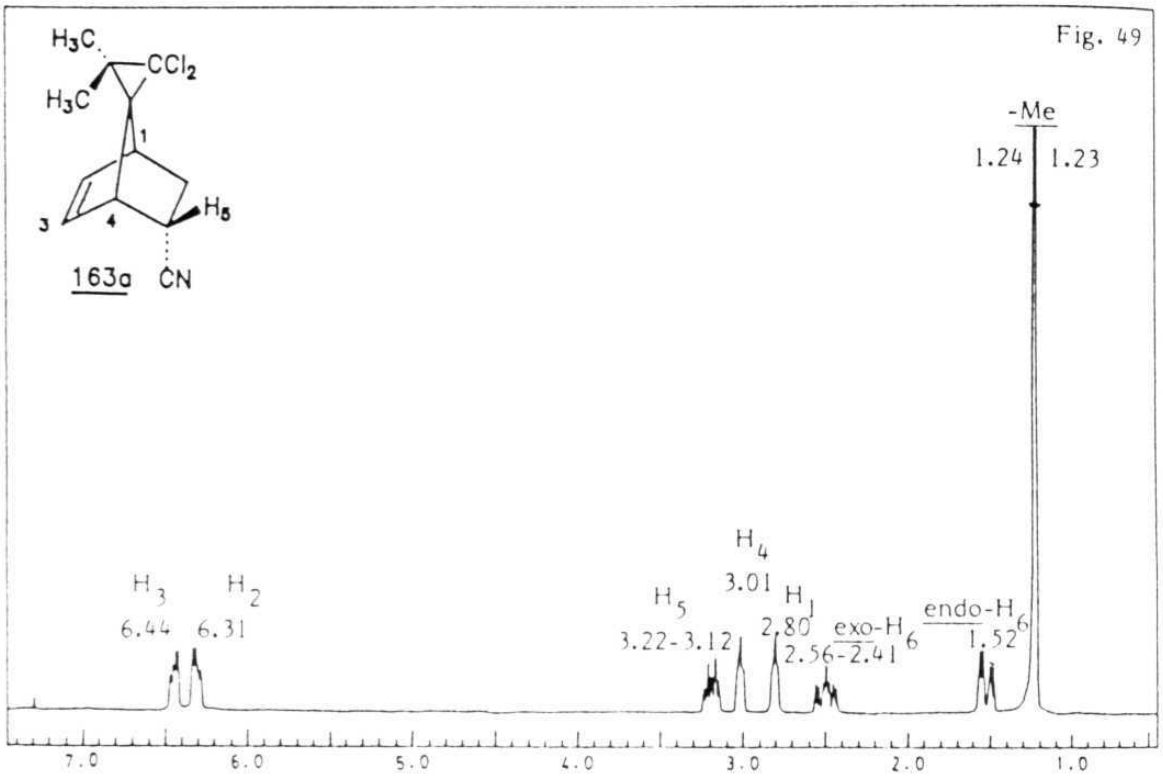
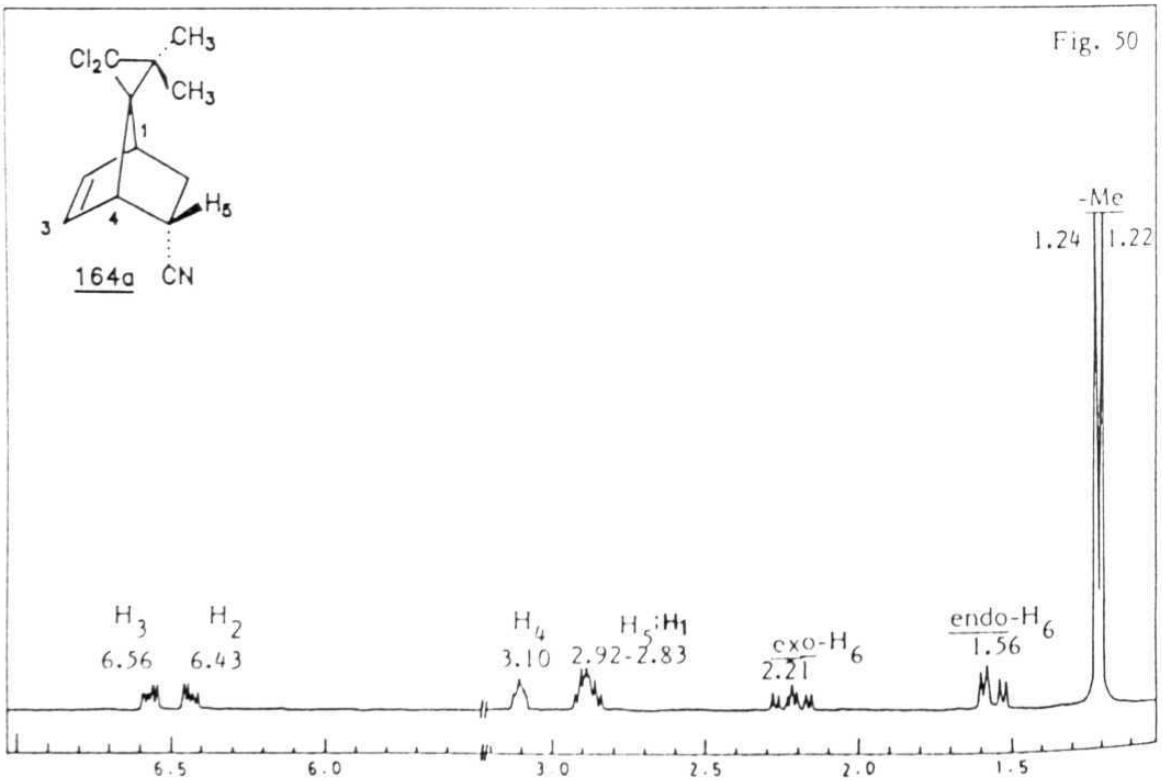

HO
CH3
4
6
1
H2
160b COOMe
Fig. 48
-COOMe
3.68
-Me
1.90
H
C=C
5.12
C=C
5.01
H
H1
H2 2.39
2.90-2.78
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Fig. 49

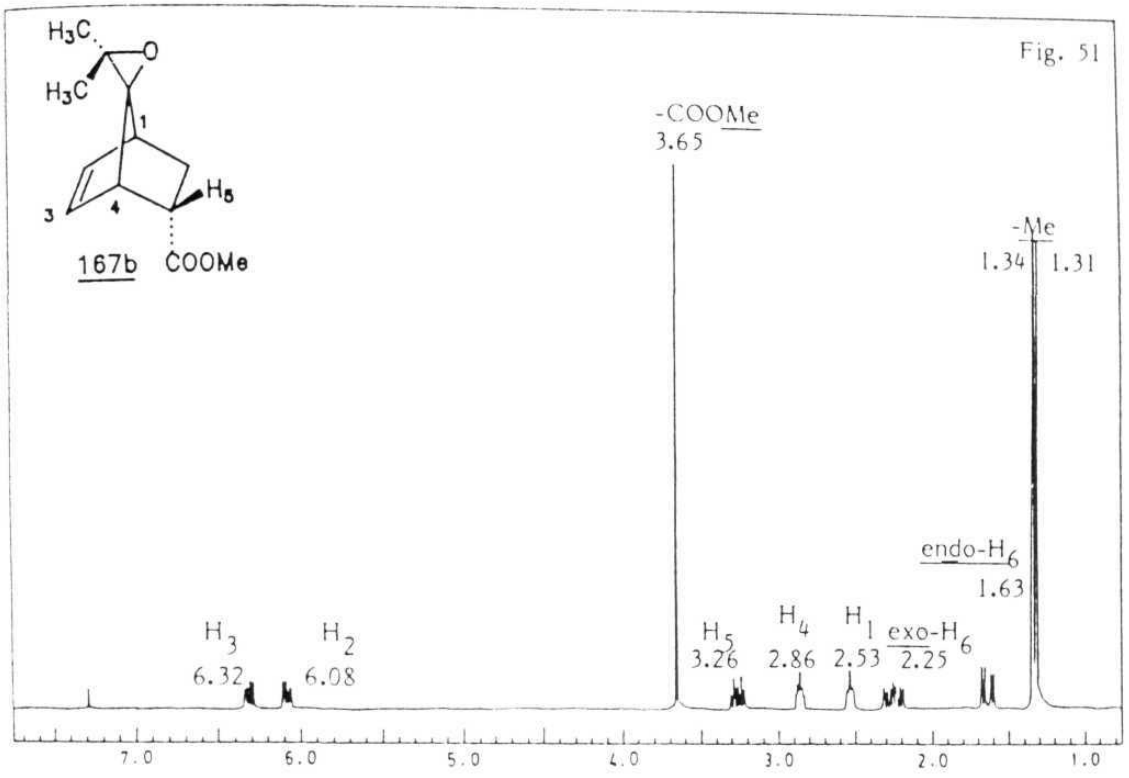


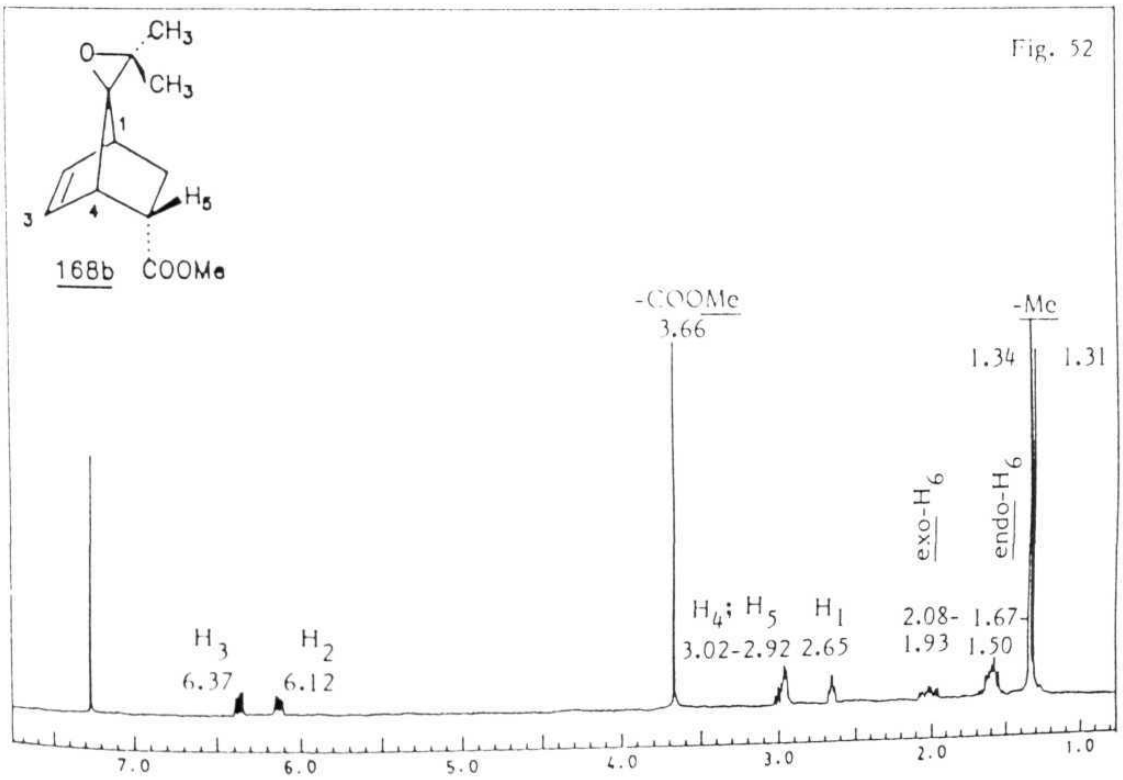
163a

Fig. 50



164a


H3C
O
H3C
1
3
4
H5
167b COOMe
Fig. 51
-COOMe
3.65
-Me
1.34 1.31
endo-H6
1.63
H3
6.32
H2
6.08
H5
3.26
H4
2.86
H1
2.53
exo-H6
2.25
7.0
6.0
5.0
4.0
3.0
2.0
1.0


CH3
O
CH3
1
3
4
H5
168b COOMe
Fig. 52
-COOMe
3.66
-Me
1.34 1.31
exo-H6
endo-H6
H4; H5
3.02-2.92
H1
2.65
2.08-
1.93
1.67-
1.50
H3
6.37
H2
6.12
7.0
6.0
5.0
4.0
3.0
2.0
1.0

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VITAE

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List of Publications:

1. Electronic control of π-facial selectivities in nucleophilic additions to 7-norbornanones, G. Mehta and F.A. Khan, J. Am. Chem. Soc., 1990, 112, 6140.
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