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The diastereoselectivity of some novel organic reactions

Zhang, Xiao-An

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The Diastereoselectivity of some Novel Organic Reactions

Submitted by Xiao-an Zhang

for the degree of Doctor of Philosophy of

the University of BATH

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I must acknowledge with thanks the financial support and sponsorship that this research project received from ministry of education of China (P.R.C.) and Park-Davis Research Unit..

I would like to place on record my appreciation of excellent technical services provided by Mr. R. F. Betteridge, Mrs. S. A. Boucher, Mr. D. F. Wood, Mr. C. Cryer and Mr. A. K.Carver as well as secretarial services provided by Mrs. G. I. Daniels.

Finally I must thank my wife Y. F. Yang for her understanding and supporting me during the course of this research, and much help to my thesis.

ABSTRACT

The work described in this thesis was carried out between October 1984 and July 1987. Some of the work was done in collaboration with Mr. A. P. Taylor (Part One).

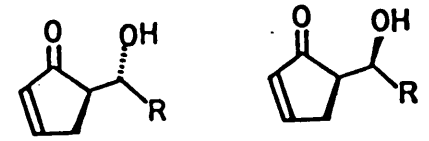
The work involves (A) a systematic study of regio- and diastereo-selectivity in aldol reactions of cyclopent-2-enone, 2-(5H) furanone and their derived trimethylsilyloxydienes and (B) diastereoselective synthesis of 1-amino-1-cyclopropyl carboxylic acid (ACPC) derivatives.

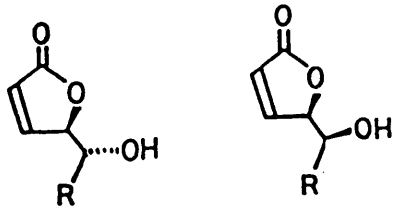
In part (A), the differences in erythro-threo selectivity were assessed for aldol condensations of aldehydes with the lithium salts of cyclopent-2-enone and 2-(5H)furanone, and for Lewis-acids catalysed condensations with the derived trimethylsilyloxydienes.

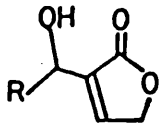
New methods for regio- and diastereoselective preparations of the aldol adducts of cyclopentenone and 2-(5H)furanone have been developed and a series of new compounds (I-IV) have been prepared by these methods. Some natural products and key intermediate compounds (V-VII) for natural product syntheses have been made. Novel compounds (VIII-X) were obtained as side-products.

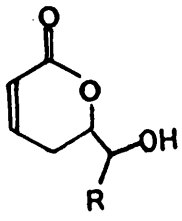
In part (B). Several routes towards to the synthesis of ACPCs have been explored and one successful method has been

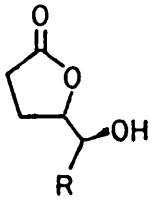
developed. Several novel ACPC derivatives (XI) have been prepared by applying this method. Novel compounds (XII-XX) were also obtained as desired or side products during this research.

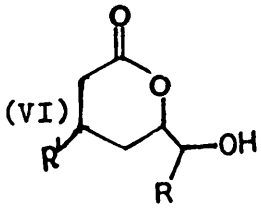
(I)  R = Me, Et, i-Pr, Ph, Bz, C_5H_{11}, , $C_{10}H_{21}$

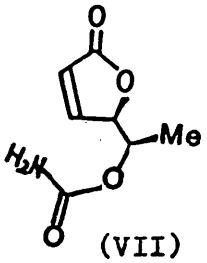
(II)  R = Me, Et, i-Pr, Ph, C_5H_{11}, $C_{10}H_{21}$

(III)  R = Me, Et, i-Pr, Ph

(IV)  R = C_5H_{11}

(V)  R = Me
R = C_5H_{11}
R = $C_{10}H_{21}$

(VI)  R = $C_{10}H_{21}$; R^1 = H
R = C_5H_{11}; R^1 = SO_2Ph



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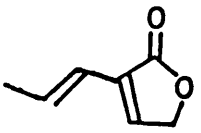

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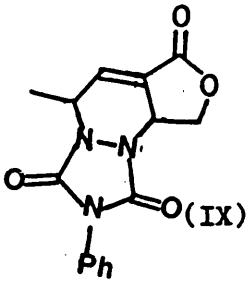

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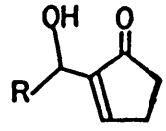
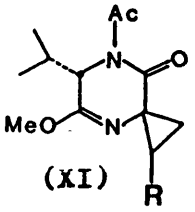


(X)

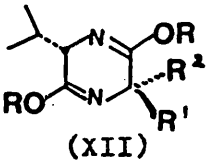
R = Ph



(XI)

R = Ph

R = p-AcOC$_6$H$_4$-



(XII)

R^1= R^2 = SPh;R=Me

R^1= R^2 = SO_2Ph;R=Me

R^1=R^2=H; R=Et

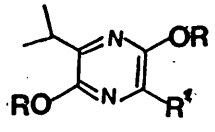
R^1=SPh;R^2=H;R=Et

R^1=SPh;R^2=H;R=Me

R^1=SO_2Ph;R^2 =H;R=Et

R^1=SO_2Ph; R^2=H;R=Me

and their diastereo-isomers.



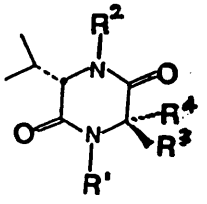
(XIII)

R=Me; R^1=H

R=Et; R^1=H

R=Me; R^1=SPh

R=Me;R^1=SO_2Ph



(XIV)

R^1=R^2=R^3=R^4=H

R^1=R^2=Bz;R^3=R^4=H

R^1=R^2=Bz;R^3=Me;R^4=H

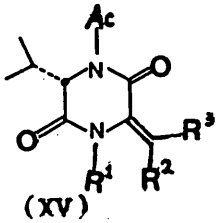
R^1=R^2=Bz;R^3=SPh;R^4=H

R^1=R^2=Bz;R^3=R^4=SPh

R^1=R^2=Bz;R^3=SO_2Ph;R^4=H

R^1=R^2=Bz;R^3=R^4=SO_2Ph

R^1=R^2=Ac; R^3=R^4= H



(XV)

R^1=H; R^2=Ph; R^3=H

R^1=H; R^2=Me; R^3=H

R^1=H; R^2=H; R^3=Me

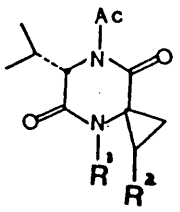
R^1=H;R^2=p-HO-C$_6$H$_4$;R^3=H

R^1=H;R^2=p-AcO-C$_6$H$_4$;R^3=H

R^1=Ac;R^2=Ph;R^3=H

R^1=Ac;R^2=Ph;R^3=Me

R^1=Me;R^2=MeO-C$_6$H$_4$-;R^3=H

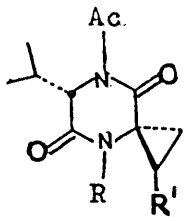


(XVI)

R^1=Me; R^2=Ph

R^1=Me; R^2=p-AcO-C_6H_4

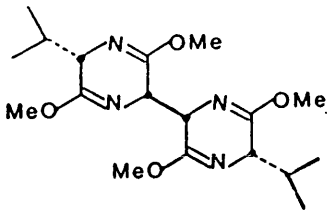
R^1=H; R^2= Me



(XVII)

R=Ac; R^1=COOMe

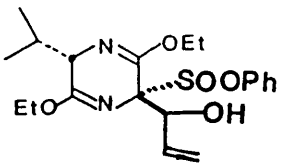
R=H;R^1=COOMe



(XVIII)

Trans-Trans dimer

and Trans-Cis dimer



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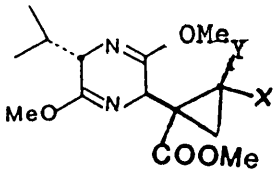


(XX)

X = Br; Y = COOMe

X = COOMe; Y = Br

FOREWORD

The Arabic numerals parenthesized in the text refer to the diagrams of formulae while the square bracketed Arabic numerals indicate references to the bibliography.

The following abbreviations occur in the text:

Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
Bn	Benzyl(Bz)
Boc	tert-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
C.I.	Chemical Ionization
mCPBA	m-Chloroperoxybenzoic Acid
CSI	Chlorosulfonyl isocyanate
DCM	Dichloromethane
DIBAH	Diisobutylaluminum hydride
DME	1,2-Dimethoxyethane (glyme)
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Gly	Glycine
Glyme	(see DME)
GLC	Gas-Liquid-Chromatography
HPLC	High Pressure Liquid Chromatography

HMPA	Hexamethyl phosphoramide (Hexamethyl phosphoric triamide)
HMPT	Hexamethyl phosphorous triamide
HOAc	Acetic acid
IR	Infrared
LDA	Lithium diisopropylamide
Me	Methyl
m/e	Mass to charge ratio
mg	Milligram
ml	Millilitre
mmol	Millimole
MP	Melting point
MS	Mass spectrum
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
Pr	Propyl
Py	Pyridine
Rf	Retention index for thin layer chromatography
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl(or Tetramethyl silane)

Tos	p-Toluenesulfonyl
Trif	Trifluoromethyl sulfonate
UV	Ultraviolet
Val	Valine

CONTENTS OF PART ONE

INTRODUCTION

RESULTS AND DISCUSSION

CONTENTS OF PART TWO

PART ONE

Regio- and Diastereoselectivity in Aldol Reactions of Cyclopent-2-enone, 2-(5H)-Furanone and their derived Trimethylsilyloxydienes

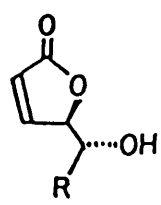
INTRODUCTION TO

PART ONE

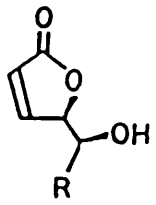
Chapter one : Introduction

1-1. Objective:

α,β-Unsaturated γ- or δ-lactones (I,II,III) have commanded increasing attention in recent years not only because they occur as natural products, but also because they are potentially important synthons.



(I)



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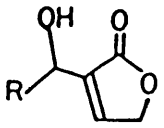
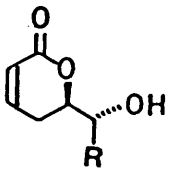
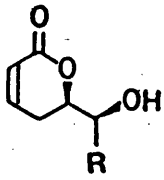


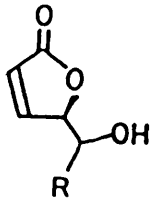


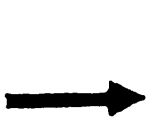


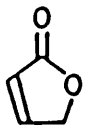
(III)

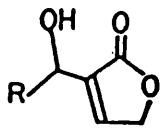
As (I) and (II) can in theory be obtained via directed aldol addition reactions between butenolide (IV) and aldehydes (Scheme 1),

Scheme 1







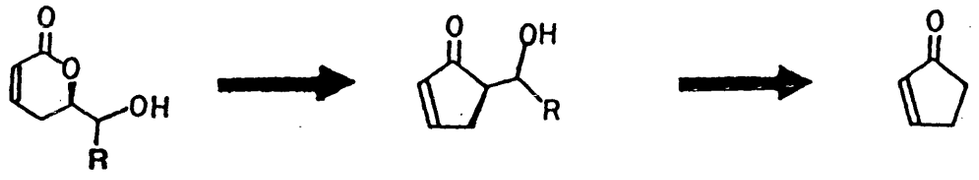


(I) (IV) (II)

and (III) could be generated via an oxygen insertion on 2-cyclopentenone aldols (V), these being obtained from

stereoselective aldol reactions (Scheme 2), it is necessary to

Scheme 2



(III) **(V)** **(VI)**

briefly review some previous work on the stereoselectivity of aldol reactions. As our research is more concerned with cyclic stereoselection, more examples are described of cyclic ketone enolate than acyclic ones. For a more general treatment of the subject, the reader is referred to several excellent reviews[1].

1-2. The background to the aldol reaction

The aldol reaction is among the oldest classes of reaction in organic chemistry and is one of the most versatile methods of carbon-carbon bond formation in organic synthesis[1,2]. Even though this important reaction has been used for almost a hundred and fifty years, systematic stereochemical investigations were not carried out on it until relatively recently.

By application of this reaction, a vast array of natural

products have been built up from various carbonyl-compounds. However, because of difficulty in directing the coupling, the traditional reaction conditions have serious limitations. These arise because the reaction is reversible and poor conversions are obtained if the aldol product is less stable than the parent carbonyl compound. In addition, the reverse reaction catalysed by acid or base generates regioisomeric enols or enolates, which in turn attack the carbonyl compounds to yield a mixture of aldols. Furthermore, the aldols are often dehydrated and the resulting unsaturated carbonyl compounds may undergo Michael addition reaction with enolate anions to give a complex reaction mixture.

The solution to this problem lies in (a) the introduction of hindered, non-nucleophilic bases which allow carbonyl compounds to be converted into their enolates without self condensation[3] and (b) the regiospecific preformation of enolates which react under non-equilibrating conditions with carbonyl compounds or their acetal-derivatives[4].

1-3. Stereochemistry of aldol reaction

The most important stereochemical question in the selective aldol reaction concerns the formation of threo and/or erythro isomers of aldols or ketols. The available data, so far, indicate that one of the stereoisomers (threo or erythro) may be formed predominently under certain reaction

conditions[1c,1d] (this is especially true in the acyclic ketone system).

The stereochemical outcome of the reaction is generally rationalized in terms of the geometry of the starting enolate and reaction conditions (kinetic control or thermodynamic control)[5-11].

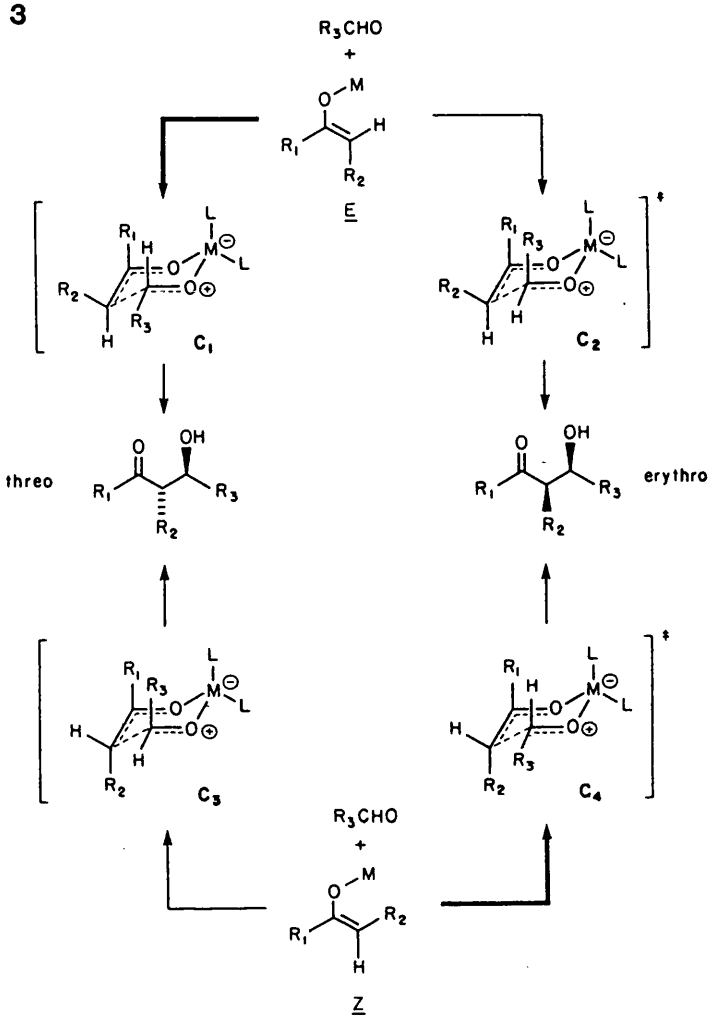
1-3-1. The stereochemistry of the aldol reaction under conditions of kinetic control

Under conditions of kinetic control, the stereoisomer formed is critically dependent on the geometry of the starting enolate. One of the first important studies to address the implications of enolate geometry on aldol product stereochemistry was reported by Dubois and Fellmann[12]. Another early extensive study was made by Evans and Heathcock[13]. In general, the (Z)-enolate gives the erythro isomer and the (E)-enolate gives the threo isomer, which can be understood in terms of the Zimmerman model illustrated in Scheme 3.

The correlation of metal enolate geometry and aldol product stereochemstry via preferred-diastereomeric chair-transition states has been widely accepted[13-15]. According to this theory in Scheme 3, for (E)-enolates, transition state C_2 is predicted to be destabilized relative to C_1 because of the R_1-R_3 1,3-diaxial interaction. In a similar fashion,

transition state C_3 is destabilized relative to C_4 for the

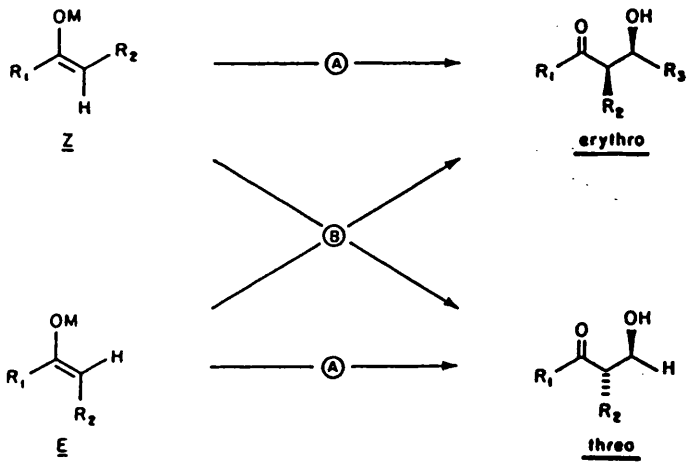
Scheme 3



(Z)-enolate[16]. It is somewhat less obvious why (E)-lithium enolates are generally less stereoselective[17a] than the isomeric (Z)-enolate. It has been argued that transition state gauche interactions between R_2 and R_3 must also be considered[14], but detailed arguments to support this contention, taking into consideration C_1 and C_2, were not provided. It has often been assumed that the steric influence of the enolate substituents R_1 and R_2

plays a dominant role in the alteration of kinetic stereoselectivity, whereas the aldehyde ligand appears to contribute to only a minor extent. Good correlation between enolate geometry and aldol stereochemistry is possible when R_1 is sterically demanding and R_2 is sterically subordinate (R_2=methyl or n-alkyl), in this case dominant path A stereoselection is observed. When R_2 becomes sterically demanding (R_2=t-Bu) path B stereoselection becomes dominant as cited in Scheme 3 and Scheme 4.

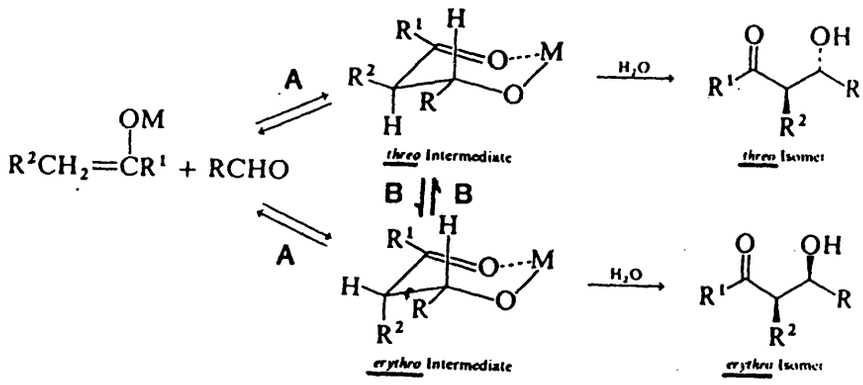
Scheme 4



1-3-2. The stereochemistry of the aldol reaction under conditions of thermodynamic control

Under thermodynamic conditions (equilibrium conditions) the threo isomer is preferred, since the more stable chairlike conformer of the intermediate metal chelate has the maximum number of equatorial substituents as indicated in Scheme 5.

Scheme 5

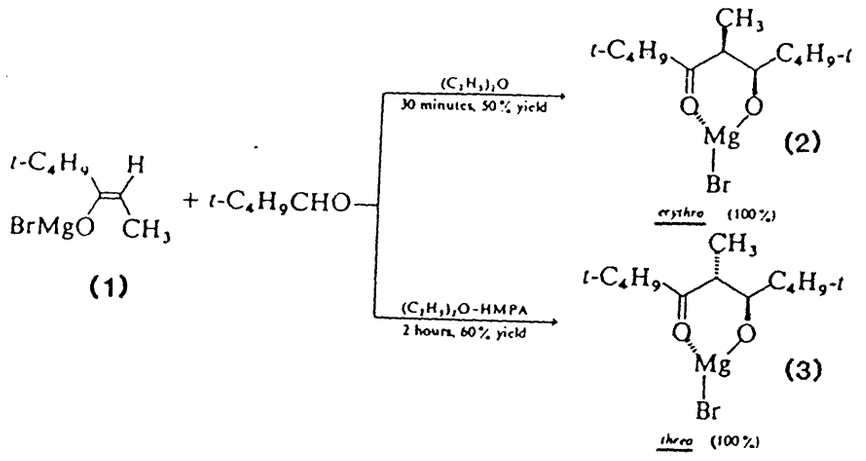


In the equilibration studies previously cited, two mechanisms for the interconversion of aldol diastereoisomers are possible, the most obvious being via a retro-aldol process[17b] (path A) in Scheme 5. In some instances, however, base-catalyzed equilibration via an aldolate (path B) is certainly possible, and such enolates are well documented as useful intermediates in synthesis[18].

A typical example is provided in the reaction of (Z)-magnesium enolate (1) with pivalaldehyde[11], as shown in Scheme 6. The reaction under kinetic control (within a relatively short reaction time) affords the <u>erythro</u> aldol, whereas under equilibrating conditions, the <u>threo</u> aldol is obtained exclusively. This result agrees with the postulate that the <u>erythro</u> chelate (2) which is formed kinetically, is converted by equilibration to the thermodynamically more

stable threo chelate (3).

Scheme 6



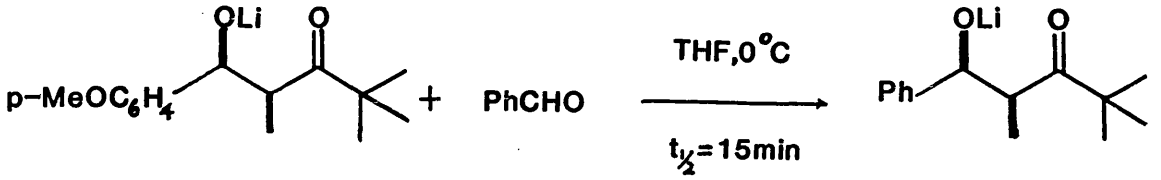
1-3-3. Some generalizations on the mechanism of the erythro-threo equilibrations

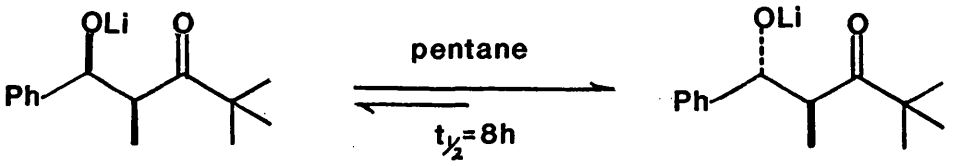
To date, literature precedents permit a number of generalizations regarding the mechanism of erythro-threo equilibrations.

First, erythro-threo equilibration may be much slower than reverse aldolization, if the enolate formation is highly stereoselective. For example, the cis enolate of ethyl t-butyl ketone has been found to show erythro-threo selectivity of 80:1 with benzaldehyde[14]. Therefore, reverse reaction of the erythro molecule is followed by conversion into the threo molecule. This is demonstrated by the equilibrations showed in Scheme 7[14].

A second generalization which may be made is that the rate of equilibration is highly solvent dependent. It has been found

Scheme 7





that erythro-threo equilibration of lithium aldolates is much faster in pentane than in ether or THF[19]. This behaviour is understandable in terms of the simple energy diagram depicted in Figure 1.

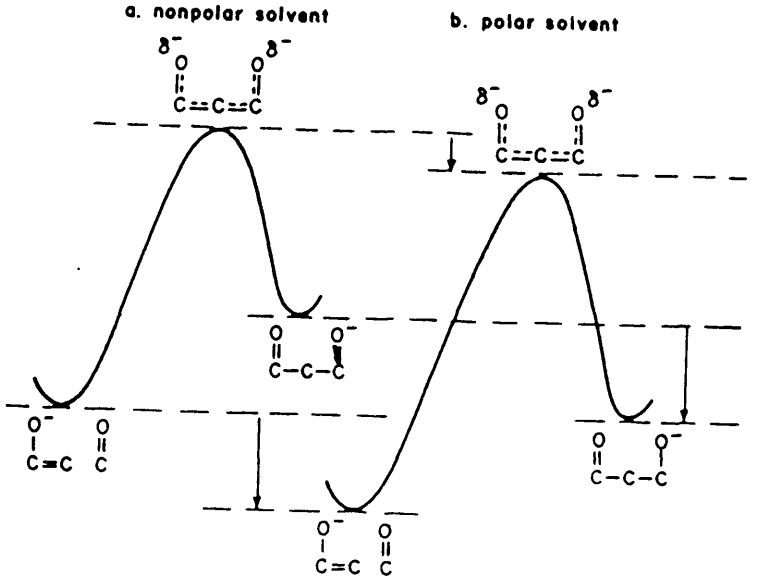


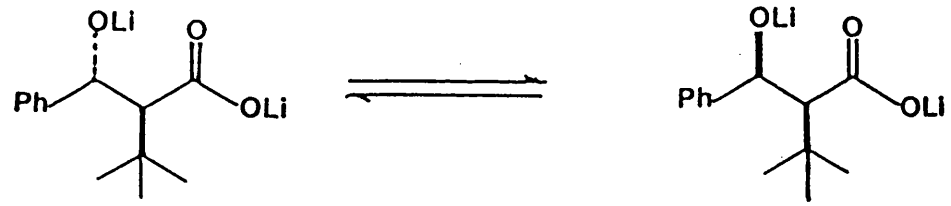
Figure I The Effect of Solvent Polarity on the Rate of the Aldol Condensation

For both the reactants and the products of the aldol condensation, the negative charge is localized on one oxygen, but in the transition state it is shared between two oxygens. A polar solvent is expected to stablize the reactants and products more than the transition state, and hence increase the activation energy for reaction. Thus, both aldol addition and aldol reversal should be more rapid in a non-polar solvent than in a polar one.

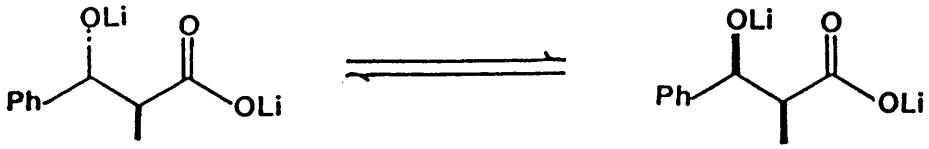
A third generalization which may be drawn is that the rate of reverse aldolization depends upon the cation which is associated with the aldolate. The higher-valent metal aldolate complexes (M = ZnL, MgL, AlL_2, BL_2), upon equilibration, appear to favour the threo diastereomer to a greater extent than the monovalent metal aldolates (M = Li, Na)[19b].

A final generalization regarding the rate of erythro-threo equilibration by reverse aldolization may be made. The rate of reaction increases with decreasing basicity of the enolates and with increasing steric repulsion in the aldolate. For example, it was found that the aldolates derived from propiophenone are much more prone to erythro-threo equilibration than the aldolates derived from alkyl ketones[14], and that aldolates (4) and (5) undergo equilibration in THF at 25^0C but that aldolates (6) and (7) do not equilibrate under these conditions[15](Scheme 8).

Scheme 8



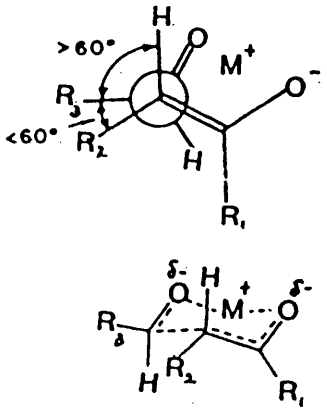
(4) (5)



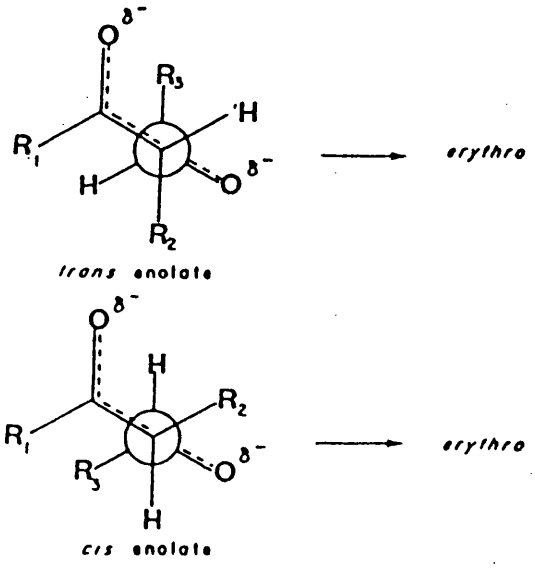
(6) (7)

1-3-4. Transition-state hypotheses

As regards the transition state hypotheses, it is worthwhile mentioning that two kinds of transition states have gained widespread acceptance.



(I) Zimmerman Transition State



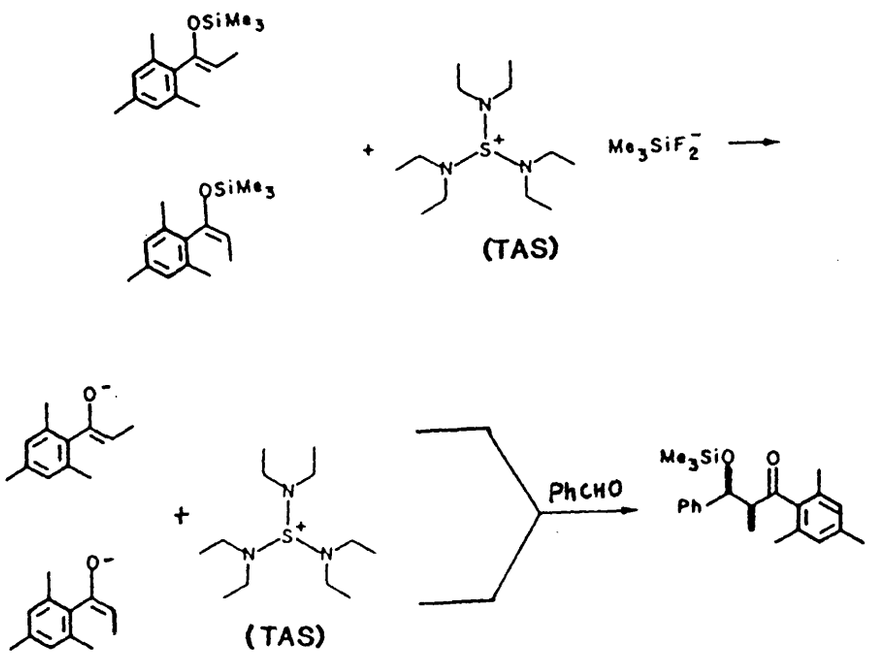
(II) Noyori Open Transition States

For reactions involving metal enolates (M = Li, MgL, ZnL, BL_2,

AlL_2, etc.), the pericyclic six-centered transition state (I) may be invoked as first proposed by Zimmerman in 1957[20] and has been supported by a considerable amount of experimental data.

For reactions between aldehydes and "naked" or ion-pair dissociated enolates, it has been proposed that, in the absence of the organizational features of Lewis acidic metals, such enolates may prefer to react via an "open" or acyclic transition state (proposed by Noyori)(II)[4]. In this kind of transition state, the two partially negative oxygens are as far apart as possible. As suggested in (II), the important interaction is considered to be that between R_2 and R_3. Thus, both the trans and cis enolates lead mainly to the erythro aldol.

Scheme 9



A typical example supporting the "open" transition state is the condensation of TAS enolates with various aldehydes which give predominantly erythro aldols, regardless of the geometry of the enolate[21](Scheme 9).

1-4 Reactions of the lithium enolate

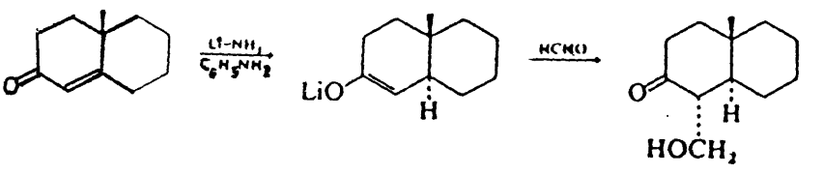
The efficiently directed aldol reaction has two main requirements. The first is the regioselective formation of an enolate from a carbonyl compound. The second is effective interception by chelation of the aldol-type adduct formed from the enolate and the other carbonyl compound. The lithium enolate satisfies the above requirements, because the enolate usually equilibrates slowly and the lithium ion can effectively trap the intermediate by stable chelate formation in an aprotic solvent such as ether or THF.

1-4-1. Generation of the lithium enolate

Regioselective or regiospecific formation of lithium enolates from unsymmetrical ketones is generally achieved by one of the following methods:

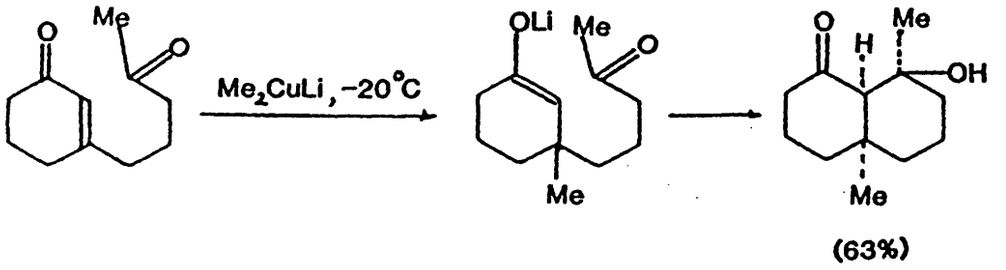
(a) Reduction of α,β-unsaturated carbonyl compounds with lithium in liquid ammonia. A typical example is shown as follows[22,23](Scheme 10):

Scheme 10



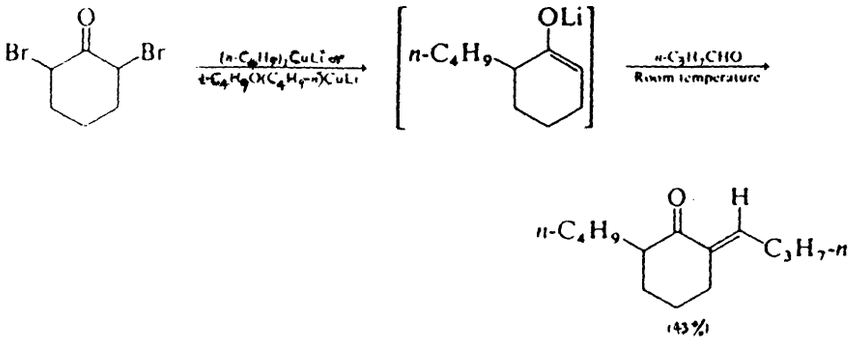
(b) Conjugate addition of organometallic compounds to an α,β-unsaturated carbonyl compounds[24] (Scheme 11)[25].

Scheme 11



(c) Cleavage of α-bromo ketone derivatives by organolithium compounds as cited in (Scheme 12)[26].

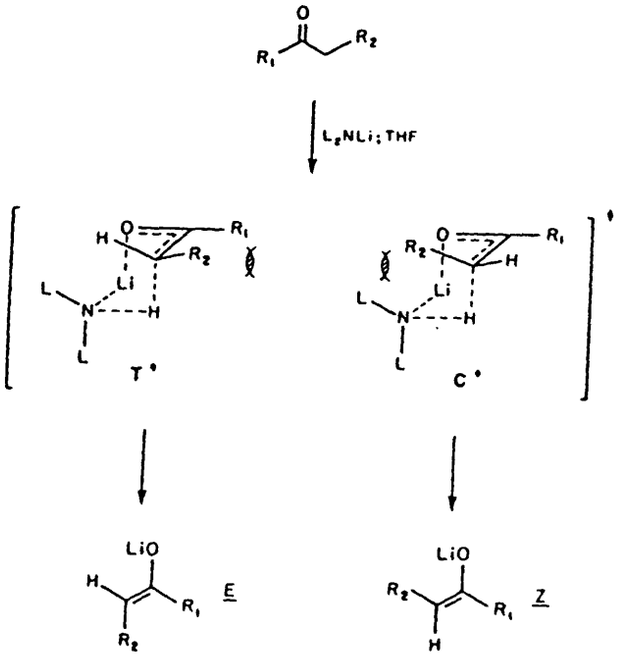
Scheme 12



(d) Deprotonation of ketones under kinetic or thermodynamic control. The sterically hindered lithium dialkylamides, such as lithium diisopropylamide (LDA), lithium hexamethyldisilylamide (LHMDS), lithium N-isopropylcyclohexylamide (LICA), lithium 2,2,6,6-tetramethylpiperidide (LTMP) are commonly used for this purpose.

The mechanism for the deprotonation has often assumed to proceed via a chair-transition state as cited in Scheme 13.

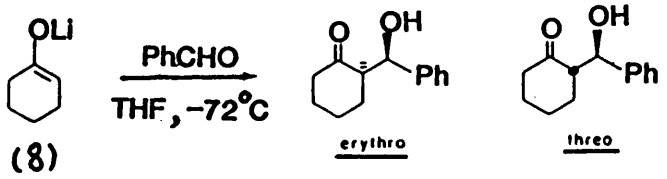
Scheme 13



1-4-2. Some examples on the diastereoselection in the aldol reaction between the lithium enolate of cyclic ketones (or lactones) and aldehydes

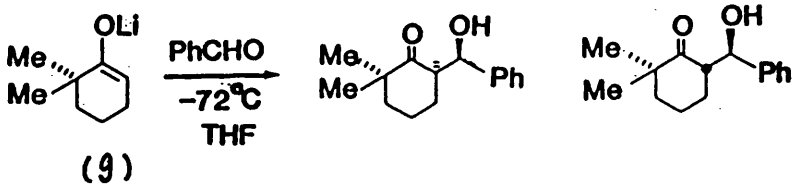
Besides the research with acyclic ketones, already described, a large number of studies have addressed the condensation of cyclic ketones with both aliphatic and aromatic aldehydes under conditions that reflect both thermodynamic and kinetic control of stereochemistry. Some reactions between the lithium enolate of cyclohexanone derivatives are shown in Scheme 14.

Scheme 14



(8)

Ratio 48:52



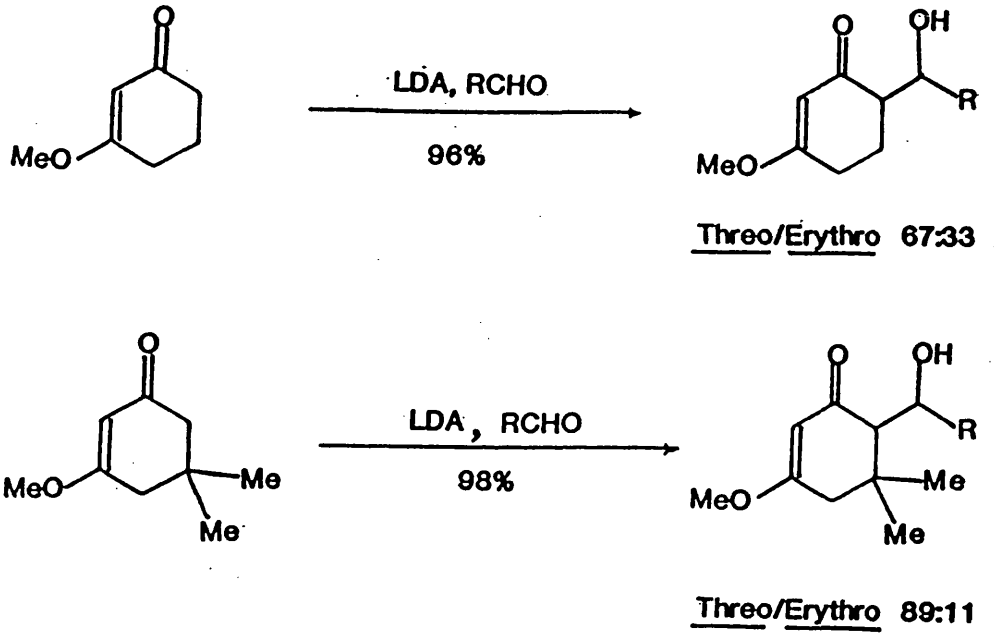
(9)

Ratio 13:87

The outcome of the kinetic process for the enolate of cyclohexanone is non-stereoselective, and with the steric effect at the enolate center, (9) gives more stereoselectivity than (8)[14,27a]. Scheme 15[27b] describes another good example which shows the effect on diastereoselectivity of steric crowding at the enolate center.

Literature searches indicate that the lithium enolate of acyclic ketones give much higher diastereoselection than that of cyclic ketones[1].

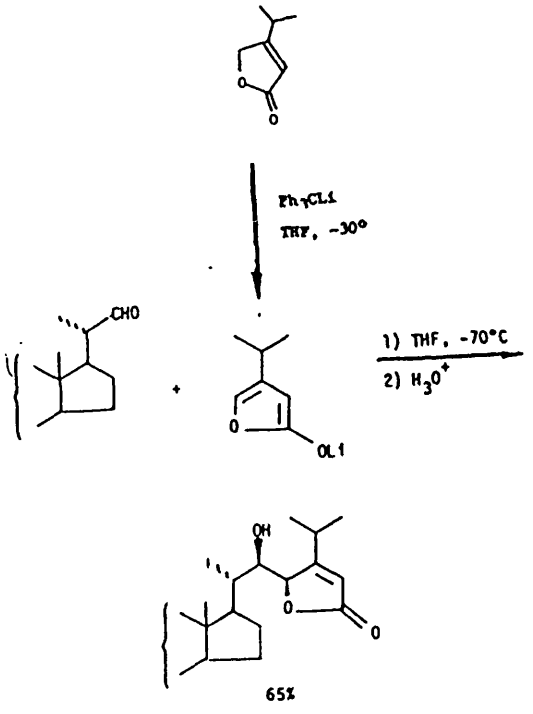
Scheme 15



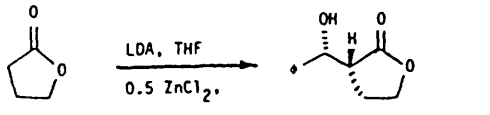
In order to improve the diastereoselectivity of aldol reactions of cyclic ketones, many efforts have been made to modify the aldol reaction from both experimental and theoretical viewpoints. Two interesting results on the aldol reactions of cyclopentanone, cyclohexanone, and 2-methyl cyclohexanone enolates with aldehydes have appeared very recently[28a,b].

Aldol reactions of saturated and unsaturated lactones have also been the subject of recent examination[28c-g]. Two examples are cited in Scheme 16.

Scheme 16



Product Converted to Brassinolide.

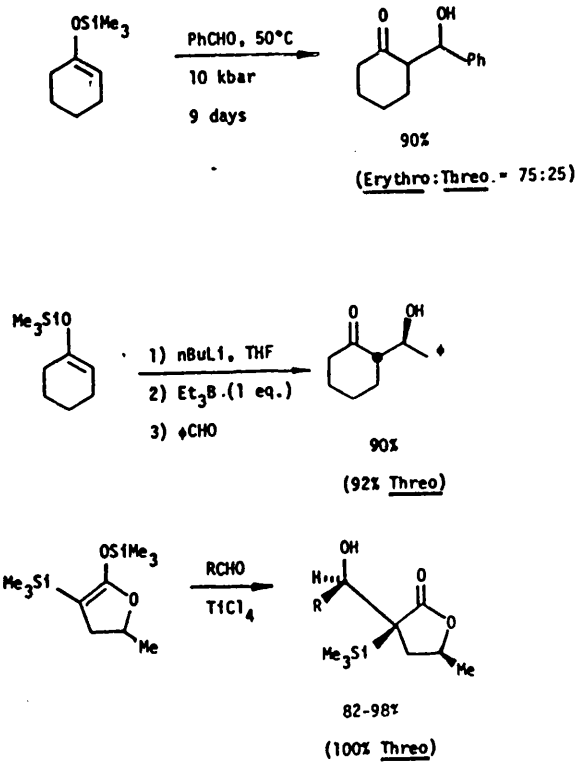


Stereoselectivity reversed with lithium cation.

1-5 Reactions of enolsilanes

A number of methods that utilize enolsilanes directly in the aldol process with either aldehydes or acetals have been developed recently (Scheme 17)[29-31]. These reactions are promoted either by suitable Lewis acids such as $TiCl_4$, BX_3, $SnCl_4$, ZnX_2, or by fluoride ion[33].

Scheme 17



Various Lewis acids for promoting the reaction between 1-trimethylsiloxycyclohexene and benzaldehyde have been examined by Mukaiyama et al.[32]. It was found that $TiCl_4$ seems to be superior to other Lewis acids with regard to chemical yield. It has been assumed that the reaction proceeds by the pathway showed in Scheme 18[32].

Regarding the stereochemistry of these reactions, variable levels of aldol diastereoselection have been noted (Table I)[32].

Scheme 18

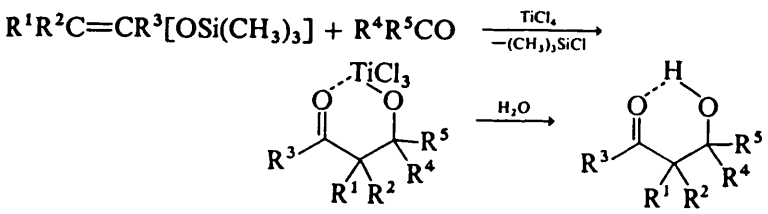
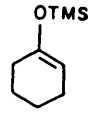
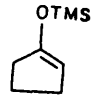


Table I

Condensation of Enolsilanes and Aldehydes

Promoted by Titanium Tetrachloride

Enolsilane	Aldehydes [at T(^{0}C)][a]	Erythro-Threo Ratio	Yield(%)
	PhCHO (-78)	1:3	92
	PhCHO (0)	1:2.5	81
	PhCHO (-78)	1:1	68
	PhCHO (0)	1:1	74
	PhCHO (-78)	1:1	95

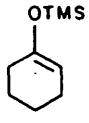
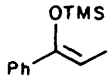
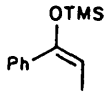
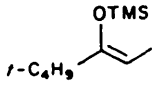
a. Reaction carried out at indicated temperature (DCM) in the presence of 1.0 equiv. of $TiCl_4$

Related reactions, catalyzed by tetra-n-butylammonium fluoride (TBAF), have been reported[33]. It is significant that the kinetic aldol condensation of this tetraalkylammonium enolate exhibits complete erythro selection as noted for the analogous lithium derivative.

Although many Lewis acids can promote the condensation of enolsilanes and acetals, trimethylsilyl triflate appears to be superior to others with regard to the diastereoselectivity of the aldols. The results of a set of representative condensations between stereochemically defined enolates and aldehyde acetals are included in Table II[4]

Table II

Trimethylsilyl Triflate-Catalyzed Condensation of Enolsilanes and Acetals

Enolsilane	Acetal	Erythro-Threo Ratio[a]	Yield (%)
	$PhCH(OMe)_2$	93:7	89
	$i\text{-}Pr\text{-}CH(OMe)_2$	86:14	95
	$n\text{-}Pr\text{-}CH(OMe)_2$	89:11	91
	$PhCH(OMe)_2$	84:16	97
	$PhCH(OMe)_2$	71:29	83
	$PhCH(OMe)_2$	95:5	94

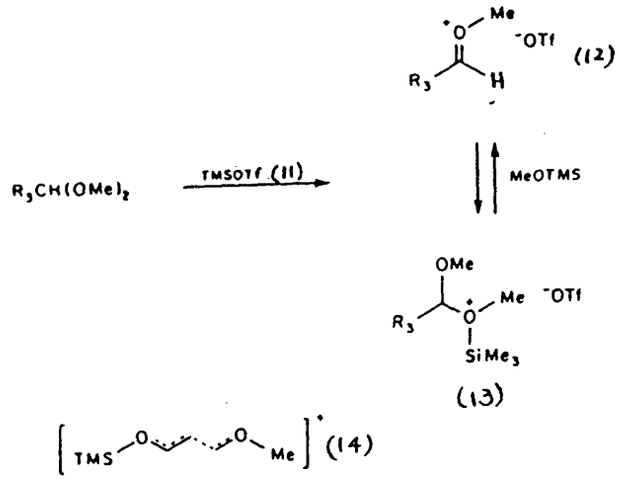
a. Condensations were carried out with 1 to 5 mol.%

TMSTf at -78^{0}C(DCM), 4 to 12 hr.

The kinetic erythro diastereoselection that has been observed from either (Z)- or (E)-enol silanes can be explained well via the Noyori Model "open" transition state.

Regarding the mechanism of this reaction, it is assumed that the role of the triflate reagent (11)(Scheme 19) is to activate the acetal with the possible intervention of either (12) or (13) as the putative electrophilic species, which undergoes reaction with the enolsilanes via the extended acyclic transition state (14).

Scheme 19



Although the majority of the work has been done on the use of preformed enolates such as lithium and silyl

enolates, it appears that considerable effort has been expended on enolates associated with other cations, partcularly boron and zinc. In addition, there have been studies involving aluminium, zirconium, and tetraalkylammonium enolates[28b].

Since these are not of direct concern to our work, they are not discussed other than by reference to several excellent reviews[1,34].

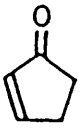
RESULTS AND DISCUSSION FOR PART ONE

Chapter 2 : The Regio and Diastereoselection of Aldol Reaction of Cyclopent-2-enone with aldehydes

2-1. The Objective:

Cyclopent-2-enone is a very useful reagent in organic syntheses as it has two functional groups from which many new functionalities can be generated. Although cyclopent-2-enone is frequently used in natural product synthesis[34b], a systematic study of its use in stereoselective aldol reactions has, until now, not been undertaken.

Since one of our interests was to develop methodology for the the synthesis of δ-substituted α,β-unsaturated δ-lactones according to Scheme 1, Chapter one, the stereoselection of aldol reactions of cyclopent-2-enone became critically important in our research and needed urgently to be assessed.



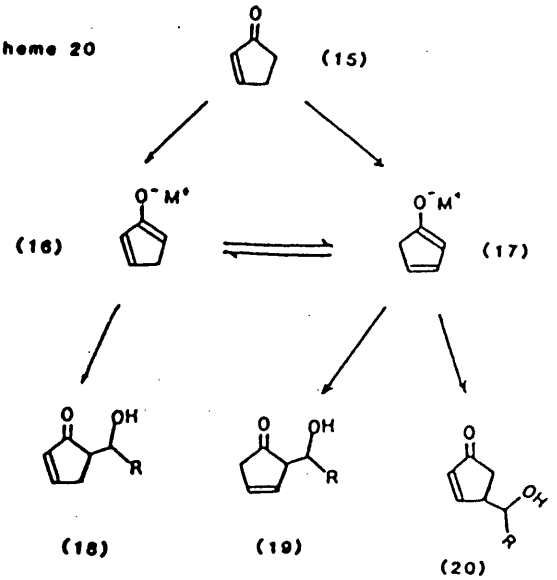
(15)

Since the starting compound (cyclopent-2-enone) was a conjugated, cyclic ketone and had the potential for generating three regioisomeric aldol products, the following difficulties

needed to be resolved.

(i) Regiospecificity of deprotonation and aldol formation.

Scheme 20



(ii) The problem of preventing equilibration of the two possible enolates (16),(17) needed to be addressed.

(iii) The tendency of the enolate and starting material to undergo a Michael addition.

Thus, reaction conditions had to be evolved to drive the enolization to completion and cause the directed cross aldol addition to take place avoiding Michael addition reaction or self-polymerization.

2-2. The structure determination of the aldol products

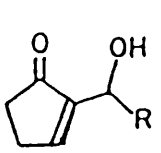
Our initial experiments were carried out using LDA as base to generate at $-78^{o}C$ a lithium enolate from cyclopent-2-enone. This was subsequently reacted with various aldehydes. After work-up involving flash chromatography, in all cases except one, a pair of diastereoisomers was isolated. A more detailed

description of the reaction procedure is in 2-4.

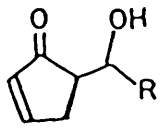
Since all the aldols obtained in this section were new, it was necessary to rigorously prove first of all their structures and then their relative stereochemistries.

2-2-1. Determination of the regio isomer

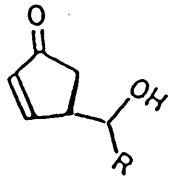
Initially, three possible structures (21),(22),(23) were considered as reaction products, according to mass spectral data and elemental analysis.



(21)



(22)



(23)

Structures of the type (21) were excluded since the ^{1}H-NMR spectra of the aldols contained signals corresponding to two protons in the alkenic region and their 135^{0}-DEPT carbon spectra showed two alkenic carbons each carrying one hydrogen.

The structure (23) was eliminated partially because of the results of infrared measurements on the aldol products in solutions of different concentration. Measurement in very concentrated solution showed a broad absorption 3550-3380 cm^{-1}. Since this was unchanged in dilute soluton (CCl_4), it suggested that strong intramolecular hydrogen bonding existed, consistent with (22) rather than (23).

The second piece of evidence against structure (23) is the the appearance of the olefinic protons as finely split pairs of triplets, J=1.5Hz. This must be due to ^{3}J and ^{4}J coupling through the $-CH_2CH=CH-$ system, identical to that observed in the starting 2-cyclopentenone.

Further evidence against the structure (23) is the chemical shifts of C(t) of our aldol products (δ 51-53 ppm) which is closer to the calculated value for C-5 for structure(22) (δ 55.7ppm) than that for C-4 of structure (23)(δ 44.9ppm).

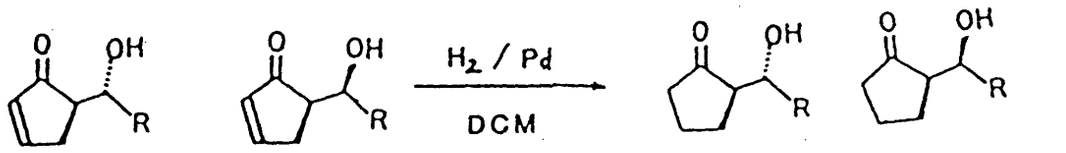
2-2-2. Distinguishing the threo and erythro isomers

Since it was extremely difficult to assign the diatereoisomeric differences simply from the data of the ^{1}H-NMR and ^{13}C-NMR spectra as the differences between these two isomers (coupling constants and chemical shifts) was very small, it was decided to prove the structures by chemical correlation with known compounds.

Firstly, the proof of the structures was obtained by reduction of the unsaturated cyclopentenone aldol to saturated (24) and (25) according to Scheme 21, which are known compounds, having been prepared by Mukaiyama et al[32] from the aldol reaction of 1-trimethylsilyloxy-cyclopentene and aldehydes as indicated

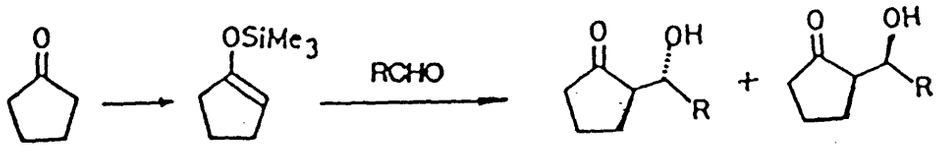
in Scheme 22. It was assumed that the stereochemistry would not be effected during the hydrogenation step.

Scheme 21



(24) R = Ph
(25) R = Bz
(26) R = $C_{10}H_{21}$

Scheme 22



(27) (28)

(24) R = Ph
(25) R = Bz

The hydrogenations went very well, and nearly quantitative yields were obtained in each case.

The hydrogenated products of our major isomers were found to have the same chemical shifts and same coupling constants as the threo isomers reported by Mukaiyama et al, as detailed in Table III.

Finally a synthetic proof of structure and relative stereochemistry was undertaken. Compound (31) is a known natural product and has been synthesized by Mori[34c] along with its diastereoisomer (threo isomer). Since the major isomer of our aldol product (29) was assigned as the threo structure, it

was relevant to convert it to the natural lactone.

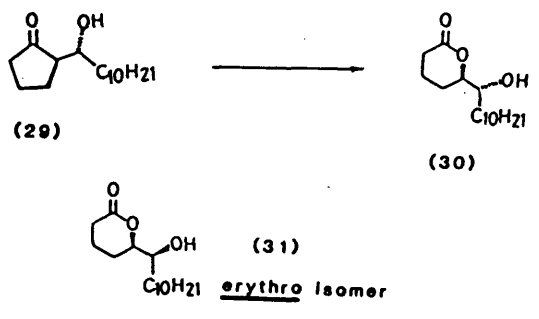
Table III

Some NMR Data for Hydrogenated products

Compound	Chemical shift(ppm) and coupling constant(Hz)	
	major isomer	minor isomer
(24)	7.20(5H, s, Ph), 4.68 (1H,d, J=9Hz, O-CH), 4.47(1H, s, OH), 1.28 -2.54(7H, broad aliphatic CH).	7.20(5H, s, Ph), 5.16 (1H, d, J=2Hz, O-CH), 3.90(1H, s,OH), 1.14-2.44(7H, broad aliphatic CH).
(25)	7.30(5H,s,Ph), 4.36(1H ,t, J=8Hz, O-CH), 2.78 (2H,d,J=8Hz,CH_2), 2.71 (1H,s, OH), 1.70-2.80 (7H, br. aliphatic CH).	7.31(5H,s, Ph), 3.85 (1H,d, J=6Hz, O-CH), 3.64(1H, s, OH), 1.3-2.89(9H,br. aliphatic)

The synthetic route was as shown in Scheme 23.

Scheme 23



Presumably, the Baeyer-Villiger oxidation would not alter the chirality at C(6) in (29) (this fact has been reported by others[46]). If our major isomer of the aldol product were erythro, we would have produced the spectroscopically identical compound to the natural product (31).

Since the product (30) obtained from our reaction (Scheme 23) was identical to the threo diastereoisomer of the natural product (31) in its IR and ^{1}H-NMR spectrum as cited in (Table IV), the major isomer of our aldol reactions was finally comfirmed as the threo isomer.

A comparison of our product with the known (31) showed that the two compounds had very different melting points but similar infrared and ^{1}H-NMR spectra, as shown in Table IV. In particular the splitting patterns of the C-6 methine protons in the resonance spectrum can be fully analysed and confirms that the two compounds have different stereochemistries at this point. Consistent with literature data[34C], which assigns the threo conformation to the isomer having the higher field carbinol methine proton, and with our chemisty, structure (30) is assigned to our product.

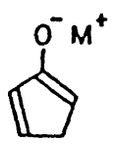
Table IV

Spectroscopic data for compounds (30) and (31)

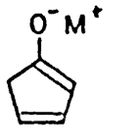
Compound	The natural product (31)(erythro isomer)	Our product (30)*
m.p. (^{o}C)	66.5-68	52.5
IR ν max (cm^{-1})	3440 (OH)	3570(s)
		3360-3550(br.s OH)
	2920(s)	2920(s)
	2850(m)	2850(m)
	1715(C=O)	1715(C=O)
	1265(O-C)(m)	1250(O-C)(m)
	1055(m)	1045(m)
^{1}H-NMR δ (ppm)	4.25(1H,dt,12Hz,8Hz)	4.20(1H,dt,11Hz,4.5Hz)
	3.82(1H,m)	3.57(1H,m)
	2.03(1H,OH)	2.6-3.20(1H,br.s,OH)
	2.57-2.66(1H,m)	2.55-2.68(1H,ddd,17Hz, 10Hz,7Hz)
	2.40-2.50(1H,m)	2.38-2.52(1H,ddd,17Hz, 10Hz,7Hz)
	1.73-2.01(4H,m)	1.70-2.04(4H,m)
	1.42-1.56(2H,m)	1.44-1.60(2H,br.s)
	1.26(16H,br.s)	1.26(16H,br.s)
	0.88(3H,t,7Hz)	0.88(3H,t,7Hz)

2-3. Regioselection in the enolization of cyclopent-2-enone

Using the arguments presented in chapter one, it was assumed that the anion (16) might be more favored under the conditions

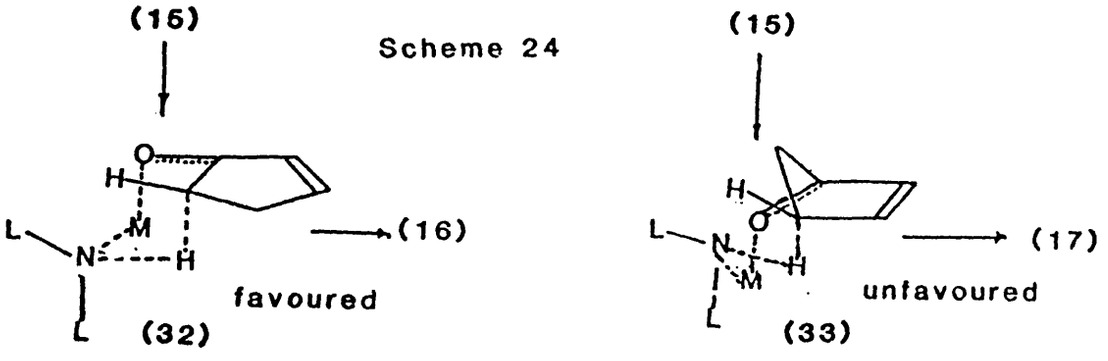


(16)



(17)

of kinetic control (LDA, THF, $-78^{o}C$) since it could be generated via transition state (32) as cited in Scheme 24.



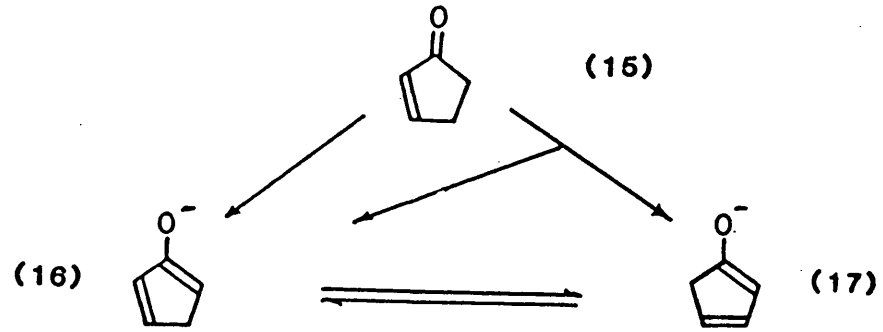
Scheme 24

Under thermodynamic conditions (higher reaction temperature, protic solvent, less strong base), it has been assumed[35] that the more conjugated enolate would generally be more favored and it would result from either an acyclic or cyclic deprotonation transition state followed by equilibration (Scheme 25).

The assumption that the enolate (17)is more stable than (16)

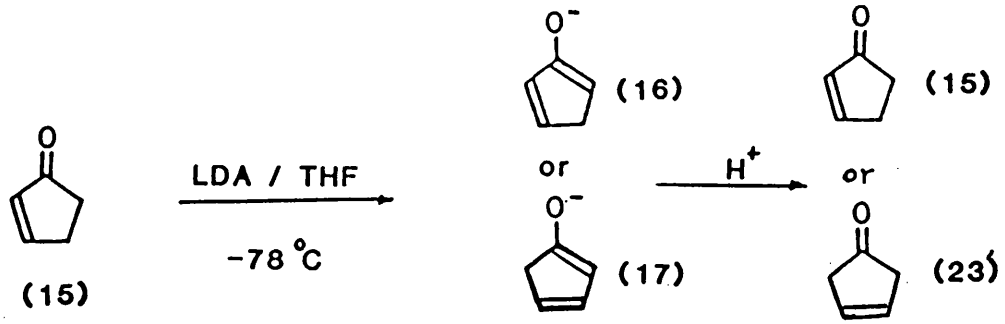
under thermodynamic conditions was based on some previous work [35]. Assuming that the fully conjugated enolate enjoys better delocalization of the negative charge it will be more favoured under equilibration conditions.

Scheme 25



Based on such an analysis, LDA was used as the base, THF as solvent, and low temperature was employed(-78°C) for kinetic control and regioselective deprotonation of cyclopent-2-enone (Scheme 26).

Scheme 26



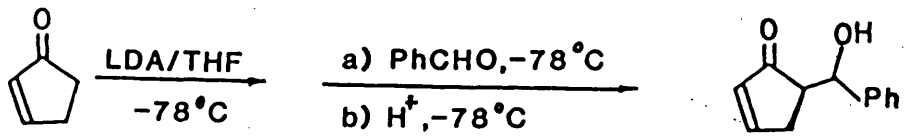
It was assumed that if the deprotonation proceeded via the chair transition state (32), the cross-conjugated enolate (16) should be formed faster. Only the starting compound (15) should be obtained after irreversible protonation of the

cross-conjugated carbanion. Otherwise, the deconjugated product (23′) might be observed.

Since no deconjugated (23′) could be generated under these conditions, it appeared that they favoured the cross--conjugated enolate (16).

Further evidence in support of this conclusion is gained from the aldol reaction between enolate (16) and benzaldehyde (Scheme 27). From it, the C(5)-aldol (34) is the only product

Scheme 27



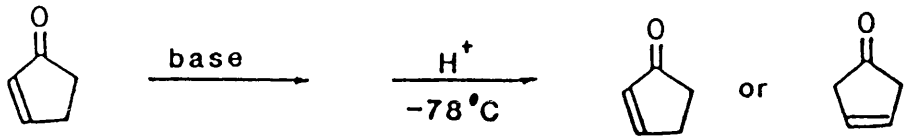
(15) **(34)**

isolated, no C(2)- or C(4)-aldol product[36] being detected.

Although it seemed that (16) was favored under kinetic conditions, the question still remained as to whether the enolate (16) was also more stable under thermodynamic conditions.

In order to solve this problem, various conditions favouring equilibration (see the deconjugation section in Chapter Three) have been examined for the reaction indicated in Scheme 28.

Scheme 28



Bases : NaH, NaOH, NaOMe, t-BuOK.

Solvent: THF, DME, Water, MeOH, t-BuOH, DMF.

Temperature: $-78^{o}C$ to RT.

Quenching reagent: NH_4Cl-H_2O, AcOH, $MeCI(Me)_2$.

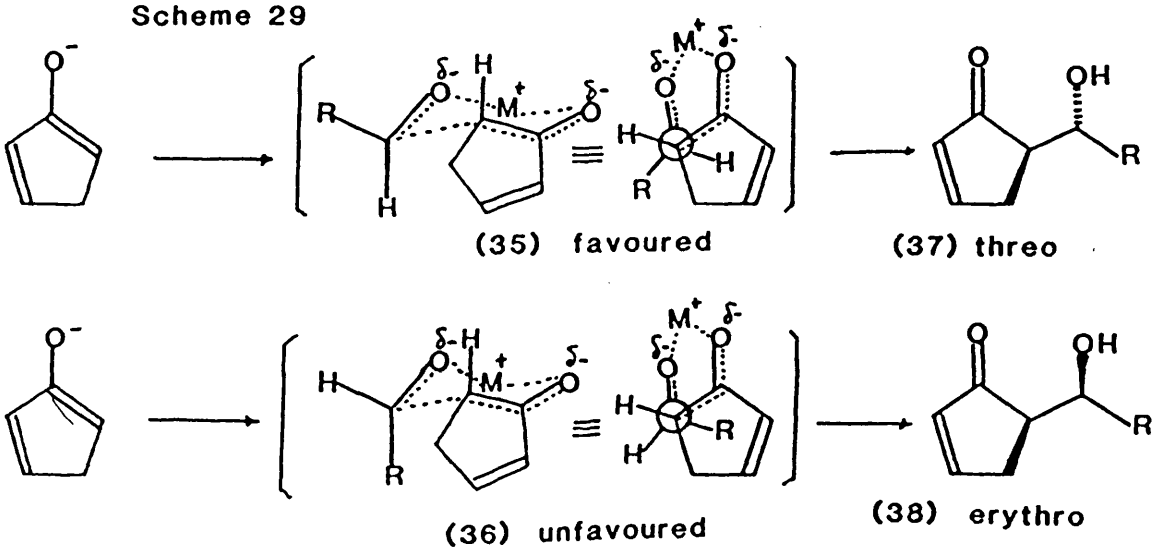
Unfortunately, these experiments were inconclusive since only resinous material and small quantities of cyclopent-2-enone were recovered. We therefore concluded that the cross conjugated enolate is the kinetically favoured anion and suspect, from a theoretical stand point, that the fully conjugated anion might be the thermodynamically favoured one.

2-4. The stereoselectivity of the aldol reaction of cyclopent-2-enone with aldehydes under base conditions

From our initial results, it was known that the formation of the cross conjugated enolate (16) was favored under kinetic conditions, but its diastereoselectivity in the aldol reaction under basic conditions was not known. As it was

assumed that the directed aldol addition proceeds via a metal chelated six-center-transition state in Scheme 29, the threo aldol was expected to predominate since (36) is destablized by the interaction between group R and the cyclopentene ring. The degree of diastereoselection of the aldol product should correspond to the bulk of the R groups.

Scheme 29



2-4-1. The diastereoselectivity of reactions with lithium enolate

In order to confirm our assumption, the following experiments (Scheme 30)(Table V) were performed by using the lithium enolate of 2-cyclopentenone with various aldehydes.

Table V

The Diastereoselectivity of the aldol reaction of the lithium enolate (16) of 2-cyclopentenone and aldehydes under conditions favouring kinetic control

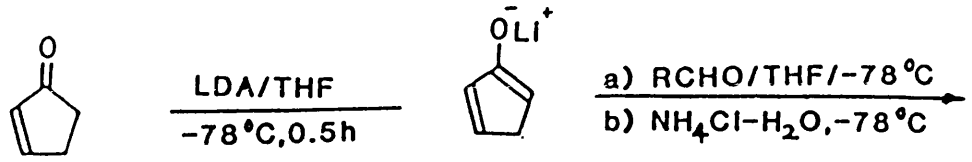
Aldehydes	Reaction time (minutes)	Aldol products Yield(%)[a]	Ratio[b] of T-/E-
MeCHO	10	67	75 : 25
EtCHO	25	64	76 : 24
i-PrCHO	10	68	93 : 7
PhCHO	25	73	76 : 24
BzCHO	25	55	84 : 16
$CH_3(CH_2)_9CHO$	25	93	82 : 19

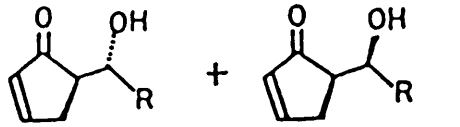
a. yield indicated here are the isolated yield.

b. the ratio was determined via GLC analysis.

The experimental results were in agreement with our expectations. Since the isopropyl group was the bulkiest, it gave the highest threo selection.

Scheme 30





threo (T-) **erythro (E-)**

(39) R= Me **(40)** R= Et
(41) R= i-Pr **(42)** R= Ph
(43) R= Bz **(44)** R= $n-C_{10}H_{21}$

The lithium cation seems therefore very efficient in binding the six-center-transition state and directing the aldol reaction.

2-4-2. The comparison of lithium cation with other metal cations

It was of interest to compare other metal cations and their ability to influence the diastereoselectivity of aldol reactions (Scheme 31), and results are listed in Table VI.

Experimental results showed that no diastereoselection was achieved by using K^+ and Na^+ under the above conditions. The Li^+ cation gives the best diastereoselection, in agreement with previous observations[1]. The lack of

diastereoselectivity with MeONa and t-BuOK could be due to

Scheme 31

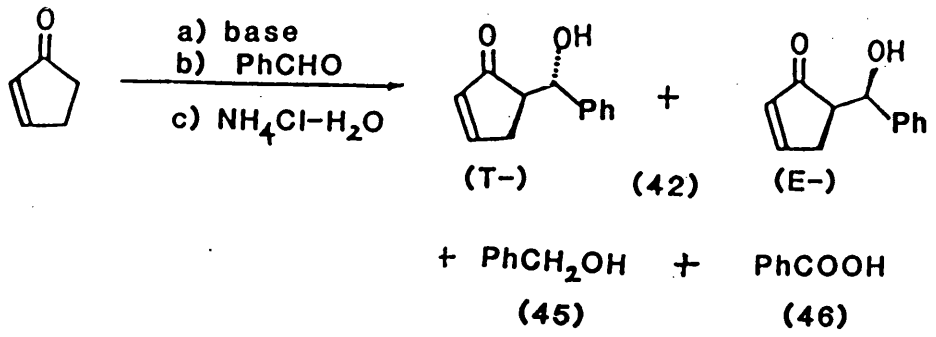


Table VI

The diastereoselection of various metal(I) enolate of 2-cyclopentenone with benzaldehyde

Base	Solvent	Reaction condition		The product (42)
		Time(hr)	T (^{o}C)	Ratio[a] of T-/E-
MeONa	MeOH	24	-78	50 : 50 [b]
t-BuOK	t-BuOK	2	RT	50 : 50 [b]
LDA	THF	0.4	-78	76 : 24

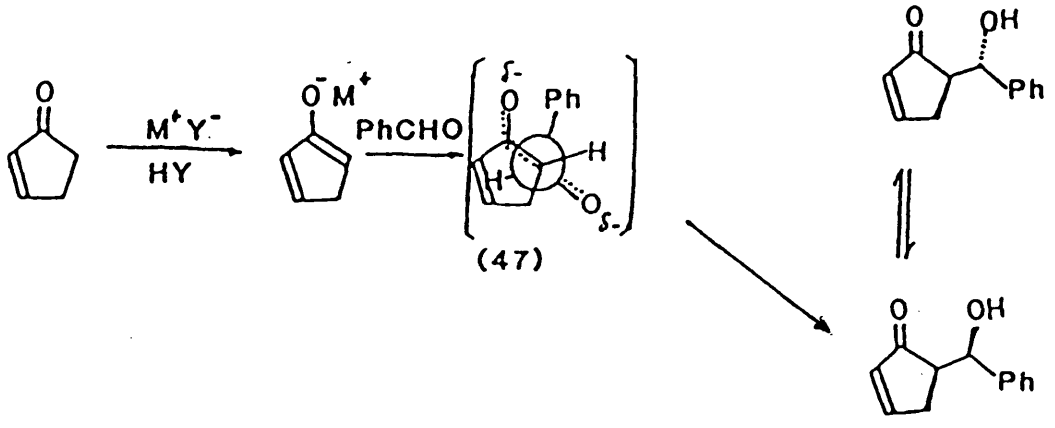
a. the ratio were determined via GLC analysis.

b. the yield of (42) was very poor and the major products obtained from such reaction conditions were (45) and (46).

either one of two reasons (Scheme 32):

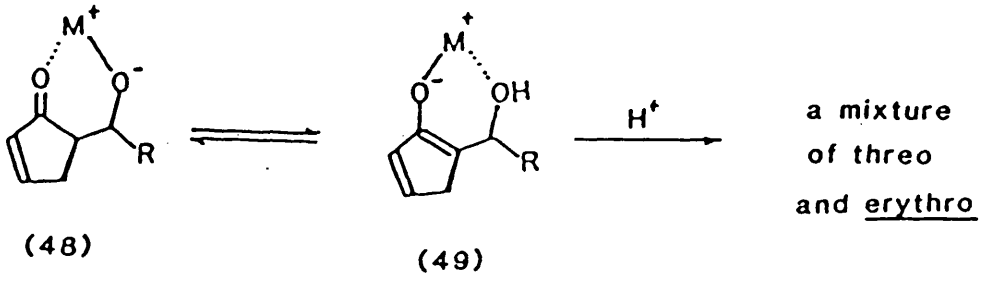
(a) the potassium and sodium ions will not trap the enolate and aldehyde well, thus , a certain amount of the reaction will tend to go via the "open" transition state leading to the erythro product;

Scheme 32



(b) base catalyzed equilibration of the product is likely under the conditions used (Scheme 33).

Scheme 33



The rate of equilibration (Scheme 33), should be related to the base strength in the order

R-OK > R-ONa > R-OLi

so that lithium salts induce the slowest rate of equilibration.

2-4-3. Some observations on the mechanism of the erythro--threo conversion

The assumption is made that the erythro-threo conversion proceeds via proton exchange equilibration as illustrated in (Scheme 33). In order to prove whether or not the equilibration is taking place, the following aldol reactions were examined under different reaction times (Scheme 34) and results are listed in Table VII.

Scheme 34

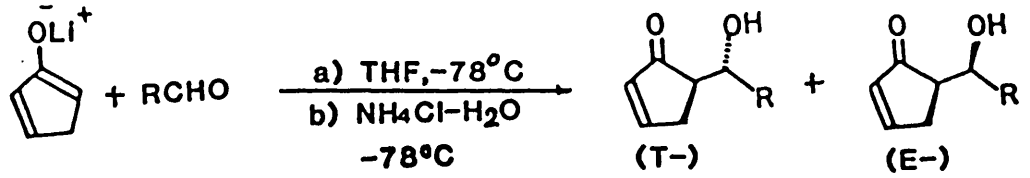


Table VII

The Diastereoselectivity of the aldol reaction under different reaction times

Aldehyde	Reaction time (minutes)	Aldol product Yield[a](%)	Ratio[b] of T-/E-
MeCHO	25	86	68 : 32
MeCHO	10	67	75 : 25
EtCHO	25	64	76 : 24
EtCHO	1	45	79 : 21

a. the yield was corrected for the recovery of starting compound determined by internal standard GLC analysis.

b. the ratio was determined via GLC analysis.

Although the change in threo-erythro ratio is small, (Table VII), it still suggests that if equilibration is occuring, it is very slow at low temperature. When short reaction times are employed, the chemical yield is relatively poor, but the diastereoselectivity is higher. This is possibly because, when the reaction time is increased, the amount of proton exchange increases leading to the aldol enolate (49) and hence to increasing levels of equilibration.

The interconversion of the threo-erythro isomers, it is thought, does not take place via a retro-aldol process since no starting compounds are detected. This suggests, therefore, that threo-erythro interconversion takes place by proton exchange via (49).

Further evidence to support the assumption that equilibration takes place between (48) and (49) are the experiments cited in Scheme 35 and Table VIII in which the threo-erythro mixture (50) of known ratio was treated with LDA in THF and quenched with aqueous NH_4Cl solution. The results are listed in Table VIII:

Scheme 35

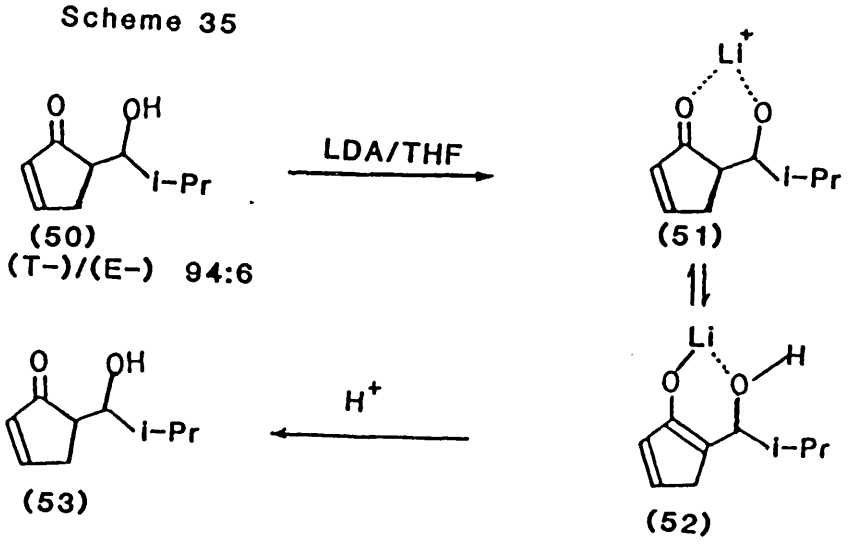


Table VIII

Starting compound	Reaction condition		Product (43)
Ratio of T-/E-	Time(hr)	T (^{0}C)	Ratio[a] of T-/E-
94 : 6	1	-78	89 : 11
94 : 6	4.5	-78	85 : 15
94 : 6	4.5	-78	
	1	RT	50 : 55 *

a. the ratio was determined via GLC analysis.

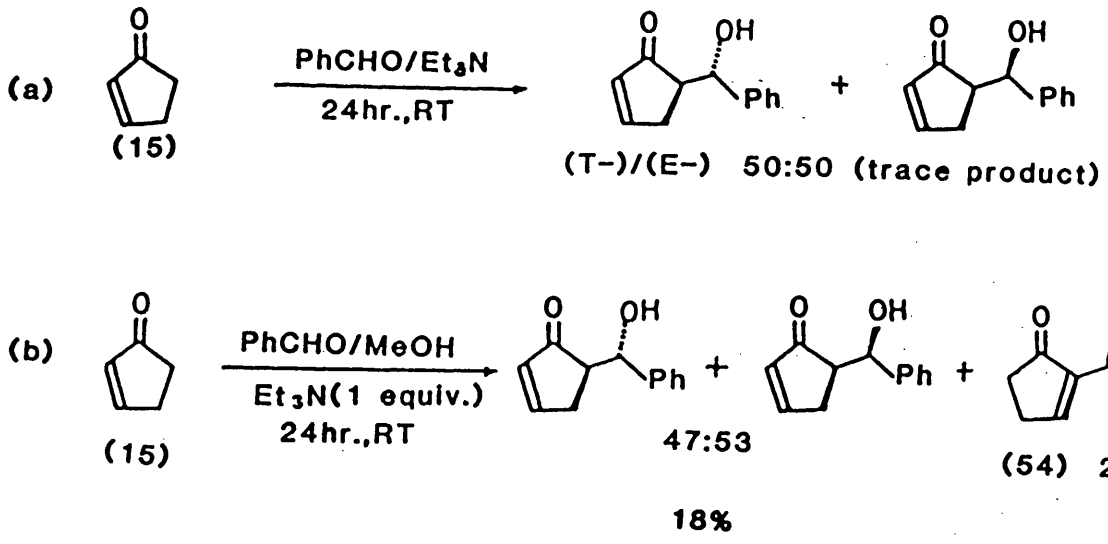
*. the chemical yield of this reaction are very poor, and most of the products are uncharacterized polymers.

2-4-4. The aldol reaction with a non-metal enolate and a proposal concerning a modified open transition state

All the foregoing data are consistent with a metal chelated chair transition state. We wished to examine one of the reactions with a non-chelating base system to find out whether erythro-selection would be favoured perhaps via Noyori 's "open" transition state (Figure II, chapter one, pp.11).

Two sets of conditions were therefore examined for this purpose as indicated in Scheme 36.

Scheme 36

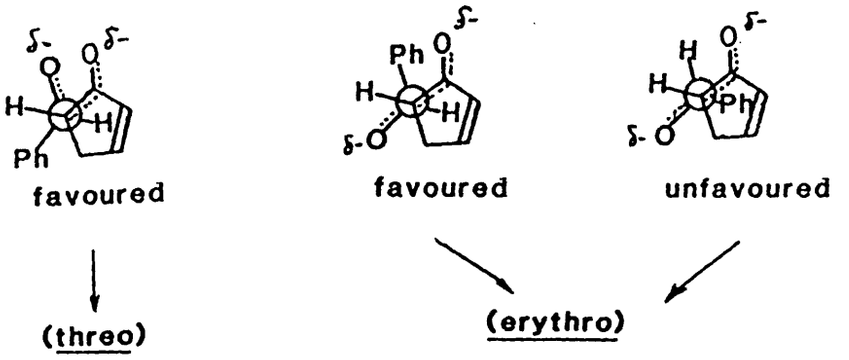


First of all no diastereoselection was observed. Since no metal is present, presumably, a "naked" enolate is formed during the reaction. If the aldol reaction were to proceed via a Noyori "open" transition state, the product should be erythro dominant. But it may be that the reaction takes place via a "Noyori transition state" to give the erythro product as

a major product and this equilibrates with longer reaction times.

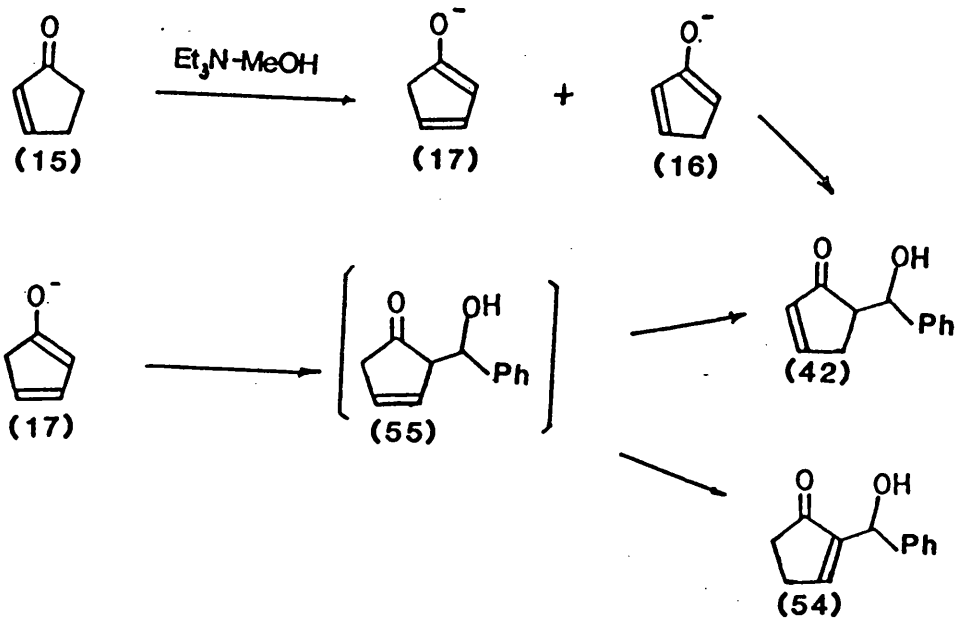
A second possible explanation of this result is that the reaction might not follow the "Noyori transition state" exactly and the steric effect of the "R" group would be the dominant factor influencing stereoselectivity, so that the two oxygens might not necessarily be as far apart as possible in the transition state (especially at the fairly high temperature), in which case, the poor stereoselection would result as cited in Scheme 37.

Scheme 37



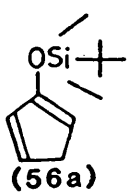
The second interesting discovery was the new product (54). Presumably, the product was generated from a "naked" extended conjugated enolate (Scheme 38). Initially, the deconjugated aldol product (55) might be formed which would be very unstable under these conditions and undergo a double bond migration to give (54).

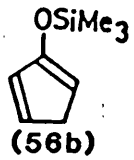
Scheme 38



2-5.The diasteroselection in Lewis acid mediated reactions of enol silyl ethers of cyclopent-2-enone with aldehydes

During the last decade, there has been a resurgence of interest in the aldol addition reaction, especially the investigation of its stereochemistry via Lewis acid mediated process[37-44] (reactions of enol silyl ether with aldehydes). In order to study the diastereoselection of aldol reactions of cyclopent-2-enone, our attention was also given to such enol silyl ethers and two compounds (56a) and (56b) were chosen for this purpose.

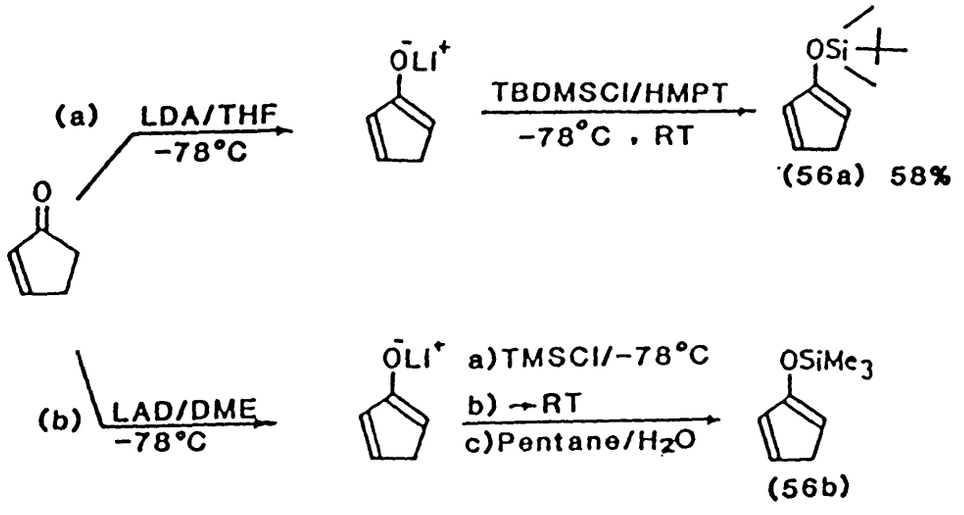

(56a)


(56b)

2-5-1. Preparation of the enol silanes (56a),(56b)

The enol silanes (56b),(56a) were prepared by quenching the corresponding lithium enolate with trimethylchlorosilane or t-butyldimethylchlorosilane. No experimental details were available in the literature for the preparation of these derivatives, the best conditions found being summarized in Scheme 39.

Scheme 39



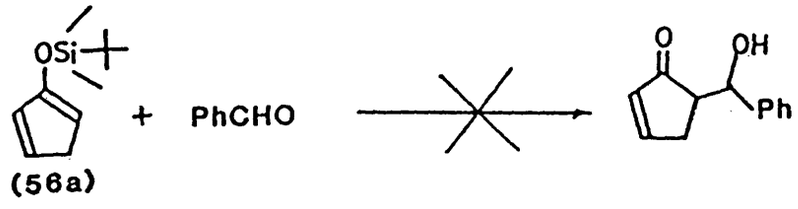
In the case of (56a), HMPT seemed to play an essential part since if the reaction was performed in its absence, (56a) could only be obtained in a extremely poor yield.

In the case of (56b), the best method required DME as solvent and dry pentane as extracting solvent for the work up of the reaction. The desired compound(56b) was obtained in fairly pure form (over 90% yield) and was used straight away for the aldol reaction without further purification.

2-5-2. The aldol reaction mediated by $TiCl_4$

Initially, (56a) was examined for the aldol reaction using various Lewis acids ($TiCl_4$, TBAF, TMS-triflate) as catalysts as cited in Scheme 40.

Scheme 40



(56a)

No aldol product could be detected in any of these reactions. The only identifiable compound isolated from the reaction mixtures was the starting silyl ether and this in only very small amounts.

Due to the failure of (56a) to react with aldehydes , the more reactive (56b) was used instead.

Since $TiCl_4$ was reported to be superior to other Lewis acids with regard to the chemical yield in such processes[45b], it was used in several reactions (Scheme 41) and the results are

listed in Table IX:

Scheme 41

(57) R=Ph
(58) R=Bz
(59) R=i-Pr
(60) R=Et

Table IX

The diastereoselection of $TiCl_4$ mediated aldol reactions

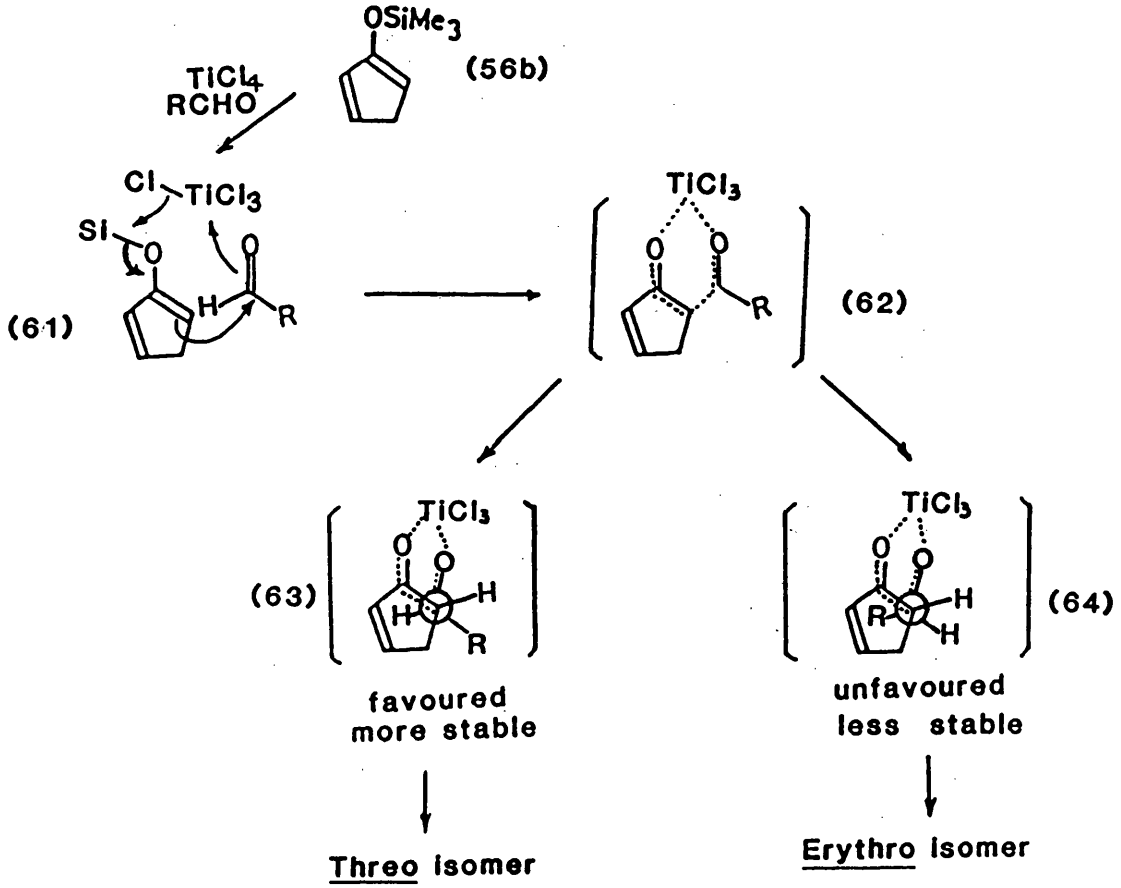
Aldehyde	The product of the aldol reaction		
	Yield(%)[a]	Ratio[b] of T-/E-	No. of compound
PhCHO	44	82 : 18	(57)
BzCHO	39	91 : 9	(58)
i-PrCHO	42	>99 : <1	(59)
EtCHO	46	86 : 14	(60)

a. overall yield from 2-cyclopentenone determined by GLC analysis.

b. ratio determined by GLC analysis.

By comparision with the LDA catalysed reactions (Table IV), the $TiCl_4$ mediated aldol reactions give higher diastereoselection, but the chemical yield is relatively poor. Presumably, the reaction would proceed via a Ti(IV) trapped cyclic transition state (Scheme 42) involving a Mukaiyama intermediate (62).

Scheme 42

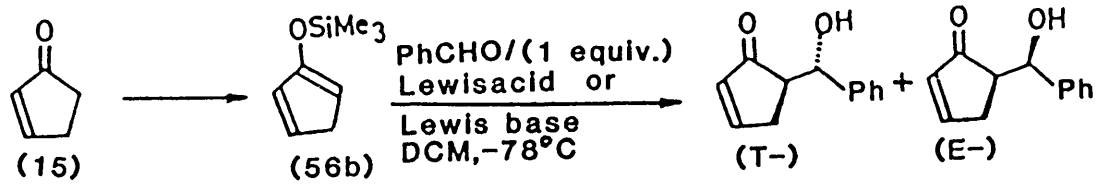


Since (63) is less crowded than (64), the reaction gives high threo selection.

2-5-3. Comparison of $TiCl_4$ with other Lewis acids and a Lewis base

A range of Lewis acids and one Lewis base were used with a view to improving the yield and diastereoselectivity of the benzaldehyde - enol silyl ether reaction (Scheme 43).

Scheme 43



and the results are listed in Table X:

Table X

The aldol reaction of (56b) with PhCHO mediated by Lewis acids or Lewis base

No	Lewis acid or Lewis base	The aldol product Yield[a](%)	Ratio[b] of T-/E-
1	$TiCl_4$	44	82 : 18
2	$SnCl_4$	56	70 : 30
3	TBAF	84	24 : 74
4	TMS-triflate	35	49 : 51
5	$AlCl_3$	63	82 : 18
6	BF_3-Et_2O	55	73 : 27
7	BCl_3	27	83 : 17
8	$Ti(O\text{-}i\text{-}Pr)_4$	4	89 : 11

a. the yield indicated here is the overall yield from 2-cyclopentenone detemined via GLC analysis.

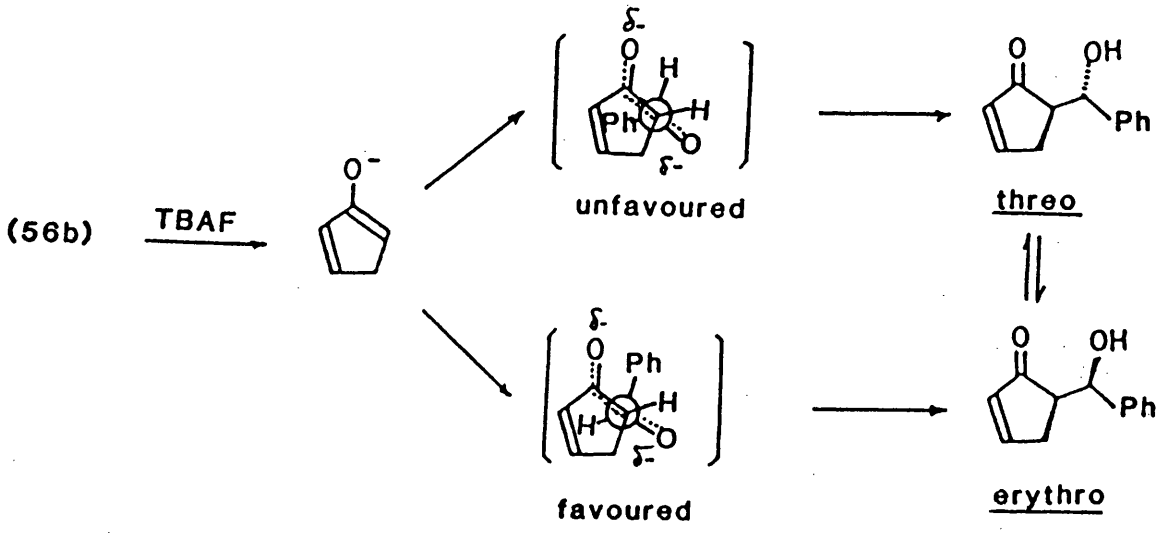
b. the ratio was determined via GLC analysis.

From Table X, it can be seen that $AlCl_3$ is superior to the others as a catalyst with regard to both chemical yield and diastereoselection and the TMS-triflate is the worst.

In all the examples of Lewis acid mediated reactions, threo selection is the norm. However when the reaction was mediated by Lewis base i.e. tetra-butylammonium fluoride (TBAF), erythro-selection takes place.

This result can be understood by invoking the Noyori "open" transition state.

Scheme 44



Presumably, a "naked" enolate was generated during the reaction and it tended to undergo aldol addition via an "open"

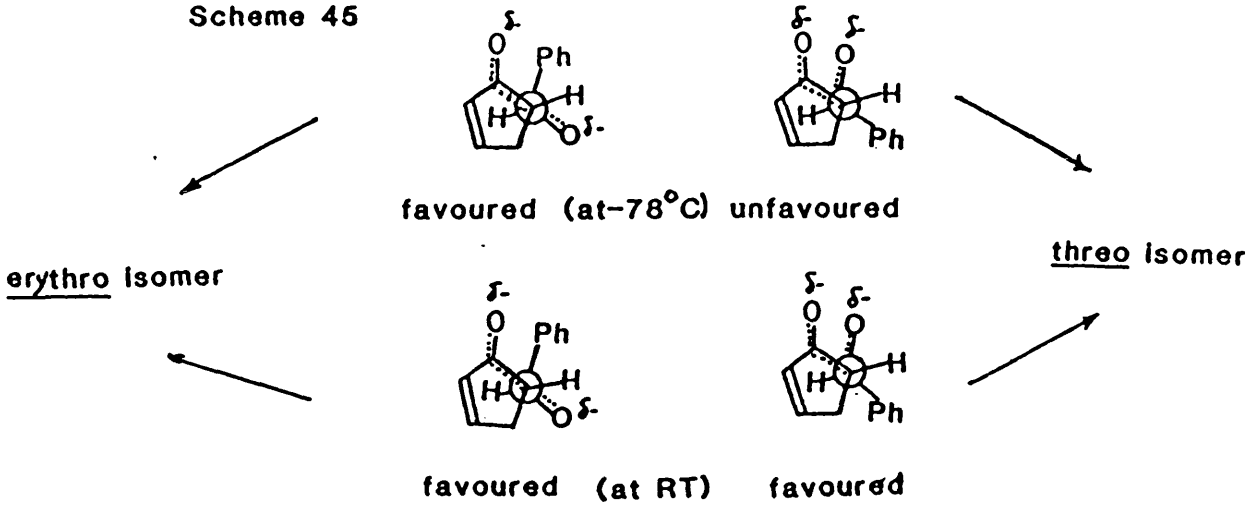
transition state leading to the erythro aldol product. The threo product (32%) could be generated either by the equilibration of the diastereoisomeric products (Scheme 33) or via the less stable "open" transition state (Scheme 44).

2-5-4. Further remarks on the proposed "open" transition state

One new question regarding the mechanism of the aldol reaction of the "naked" enolate arises here which requires an explanation. Why does the reaction sometimes follow the Noyori transition state and sometimes not?

With regard to this problem, we argue that the steric effect of the "R" group may be the dominant stereoselective factor rather than the dipole-dipole repulsion between the like partial charges on the oxygen atoms. When the reaction is carried out at low temperature ($-78^{o}C$), the destablilization caused by the proximity of the two oxygen atoms is more important since the average energy of the reactant molecules is very low, so the reaction appears to follow Noyori transition state well. But when the reaction is carried out at fairly high temperature, the effect caused by the distance between the two oxygens becomes less due to the conformation of the transition state since the average energy of the reactant molecules is higher, so the reaction will be less stereospecific as cited in Scheme 45.

Scheme 45



2-5-5. Other factors influencing diastereoselection

During the investigation, it was found that the chemical yield and diastereoselection was not only dependent on the catalyst (Lewis acid), but also dependent on other factors. Some data on the effects of varying solvent, reaction temperature and concentration are summarized in Table XI.

Possibly due to some ligand co-operation of the solvent, THF appears to be superior to DCM as a solvent for these aldol reactions with regard to the diastereoselection. When the concentration of the reactant as well as Lewis acid was smaller, the diastereoselection was increased.

Table XI*

The aldol reactions of (56b) with aldehydes under various conditions

Aldehyde	Lewis acid (equiv.)	Reaction condition			Aldol product	
		Solvent (ml)	Time (h)	T (^{0}C)	Yield[a] (%)	Ratio[b] of T-/E-
PhCHO	$TiCl_4$ (1.2)	DCM (25)	1	-78	35	91:9
PhCHO	$TiCl_4$ (1.2)	DCM (5)	1	-78	44	82:18
PhCHO	$SnCl_4$ (1.2)	DCM (5)	1	-78	56	70:30
PhCHO	$SnCl_4$ (0.1)	THF (15)	10	reflux	11	75:25
MeCHO	$SnCl_4$ (1)	THF (15)	4days	-78	60	83:17

* reaction carried out on 2 mmol. scale.

a. the yield here is the overall yield from 2-cyclopentenone determined via GLC analysis.

b. the ratio was determined via GLC analysis.

Chapter Three: The Attempted deconjugation of Cyclopent-2--enone aldol adducts, and new routes to α,β-unsaturated-δ-lactones

3-1. Objective

Deconjugation of α,β-unsaturated carbonyl or carboxyl compounds was first demonstrated by Birch[47] and has been studied by many workers[48] since then. Deconjugated 3-cyclopentenone aldols were regarded as key intermediates for lactone formation via Baeyer-Villiger oxidation. Such lactones were considered to be intermediates for unusual sugars, and considerable effort was therefore put into investigating such potential synthetic routes from 3-cyclopentenone aldol adducts.

3-2. Attempted deconjugation via a directed aldol addition

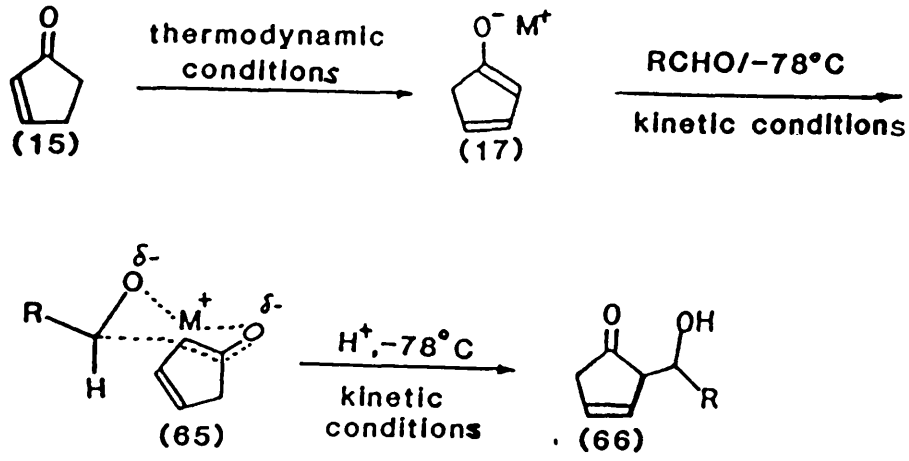
3-2-1. Via mono-anion enolate

Initially, it was assumed that the extended conjugated enolate (17) was more stable than (16) under thermodynamic conditions, although this assumption has proved to be questionable on consideration of our experimental findings. If the extended conjugated enolate could be generated under thermodynamic

conditions and the subsequent aldol reaction was carried out at low temperature (-78°C) under kinetic conditions, the deconjugated aldol addition product might result.

The reaction sequence was proposed as in Scheme 46 and results are listed in Table XII.

Scheme 46



Since no deconjugated aldol (66) nor 4-substituted product was obtained, it was assumed that the cross conjugated metal enolate might be favoured under both kinetic and thermodynamic conditions. This assumption was further supported by the reaction in which the 2-cyclopentenone was deprotonated under various metal base conditions and was reprotonated at -78°C with a range of proton-supplying reagents (see Chapter two, 2-3) and 2-cyclopentenone was the only product detected in these reactions.

Table XII

Attempted preparation of the deconjugated aldol from reaction of 2-cyclopentenone and aldehydes

No	Generation of (17)			Aldol React.		Quenching of the react.		Remarks
	Base	Solvent	T (^{0}C)	Time (h)	T (^{0}C)	Time (min.)	Reagent	T (^{0}C)	
1	MeOLi	MeOH	20 RT	0.5 1	-78	10	NH_4Cl + H_2O	-78	a,b
2	MeOLi	MeOH	-78 RT	1 1	-78	10	AcOH	-78	a,b
3	t-BuOK	DMSO + t-BuOH	0	1	-78	10	NH_4Cl + H_2O	-78	a,b
4	t-BuOK	DMSO + t-BuOH	0	1	-78	10	$MeCI(Me)_2$	-78	a,b
5	MeONa	MeOH	RT	1	-78	10	AcOH	-78	a,b
6	LDA	THF	0	1	-78	10	NH_4Cl + H_2O		a
7	LDA	THF	-78 0	0.5 1	-78	10	NH_4Cl + H_2O	-78	a
8	LDA	THF	-78 0	0.5 1	-78	10	$MeCI(Me)_2$	-78	a
9	LDA	DME	-78 0	1 1	-78	10	AcOH	-78	a
10	LDA	THF + HMPT	-78 0	1 1	-78	10	AcOH	-78	a

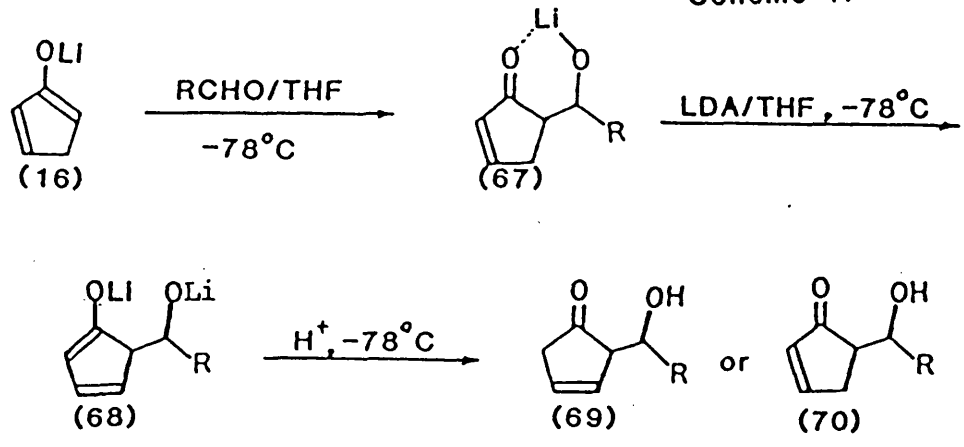
a. no deconjugated product was obtained, only C(5)-substituted, conjugated product was found.

b. some $PhCH_2OH$ and PhCOOH were detected by GLC analysis.

3-2-2. Via dianion reaction

Due to the failure to obtain the deconjugated aldol in a "one-pot" sequence, a second route was proposed as cited in (Scheme 47). It was assumed that if the lithium enolate (67) was treated with another equivalent of LDA, the less hindered C(4)-H should be deprotonated preferentially under the kinetic conditions to give the desired dianion (68) which could undergo kinetic protonation leading to the desired deconjugated aldols (69).

Scheme 47



After the reaction only the conjugated aldol(70) was obtained which suggests that the deprotonation at C(5)-H to form the cross conjugated enolate is still dominant in the reaction. This kind of deprotonation is possibly promoted by the six-center chelate indicated in Figure II.

If so, we could possibly avoid this problem via an alternative

method, i.e. generating the dianion first, then carrying

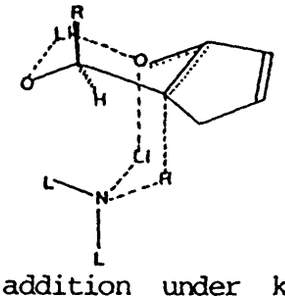
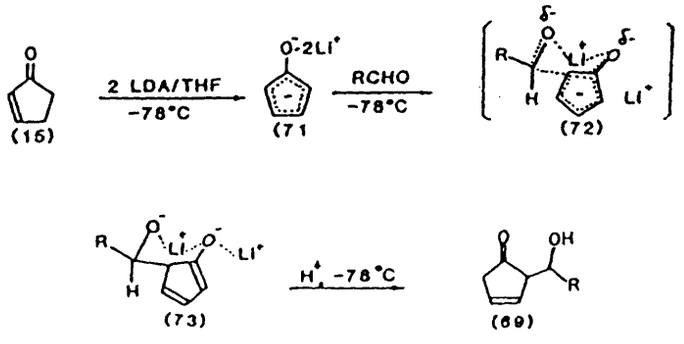


Figure II

out an aldol addition under kinetic control via a lithium trapped six-centered cyclic transition state to give the desired dianion (68) which could be subsequently converted to the deconjugated aldol product (69) as illustrated in Scheme 48.

Two experiments were performed based on this idea, one of them by preparing the dianion by using 2 equivalents of LDA at -78^0C (left standing for one hour); another was performed by preparing the mono-carbanion first at -78^0C, then adding the second equivalent of LDA at -20^0C (left standing for 0.5 hour). The aldol reactions were carried out at -78^0C, stirring for 10 minutes, before being quenched with

Scheme 48



AcOH(1 equiv.)in THF at that temperature. Since an inseparable multi-component mixture was generated in each case, it was

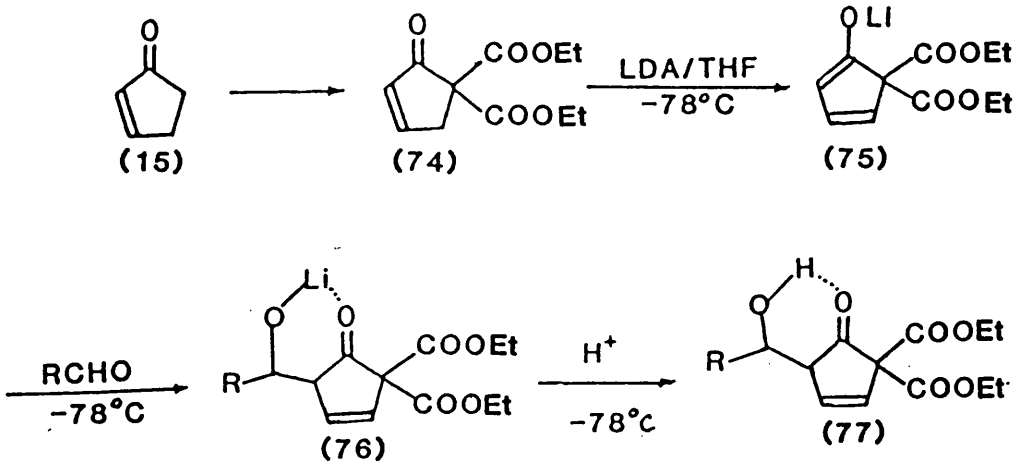
considered that this dianion was too difficult to manipulate in our proposed sequence.

3-3. An attempted indirect deconjugation

3-3-1. Initial Plan

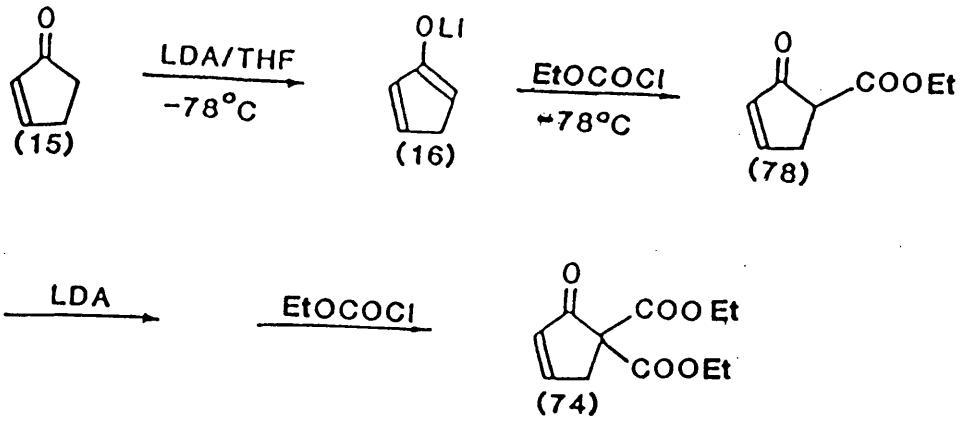
An alternative approach was proposed as cited in Scheme 49, using the dicarboethoxy derivative (74). Using this substrate only the anion with extended conjugation could result from deprotonation. If this underwent substitution at C-5, then the desired product(77) would be formed and then could undergo hydrolysis and by loss of CO_2 lead to 2-substituted 3-cyclopentenones.

Scheme 49



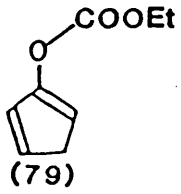
Compound (77) would be a very useful intermediate which could be converted into polyfunctional lactones. Initially, ethyl chloroformate was chosen as a carboxylating reagent, and the experiment was designed as follows (Scheme 50).

Scheme 50



3-3-2. Attempted preparation of the 2-cyclopentenone-5,5-dicarboxylate (74)

At first, one equivalent of LDA and EtOCOCl were used to prepare the mono-carboxylated compound (78). However only the O-carboxylated compound (79) was obtained.This result suggests

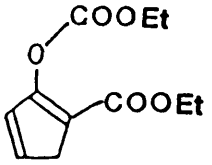


$(EtOCO)_2O$

(80)

that EtOCOCl is a fairly "hard acid" and has reacted with a relatively "hard base"- enolate oxygen of (16) - to give (79) under kinetic conditions. If a relatively "soft base" was used, or a higher reaction temperature then C-alkylation might occur. Based on such reasoning, the reagent $[(EtOOC)_2O]$ (80) was used for the same purpose. It was found that when the reaction was carried out at $-78^{o}C$, a mixture of (79) and (78) was obtained in the ratio of 88:12. When the carboxylation reaction was carried out at $-20^{o}C$, (78) was obtained as a sole product.

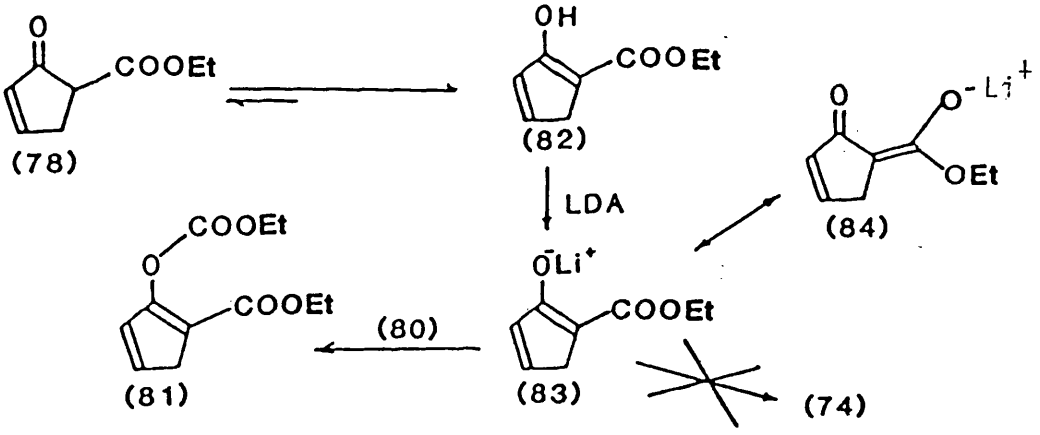
The second carboxylation reaction was carried out using (78) as a starting material by treating it with one equivalent of LDA and reagent (80) under a range of conditions (from $-78^{0}C$ to RT, 0.5 hour to 4 hours). Again, instead of the desired compound (74), the O-acylated compound (81) was the only product obtained.



(81)

In order to understand this result, the following was proposed (Scheme 51).

Scheme 51



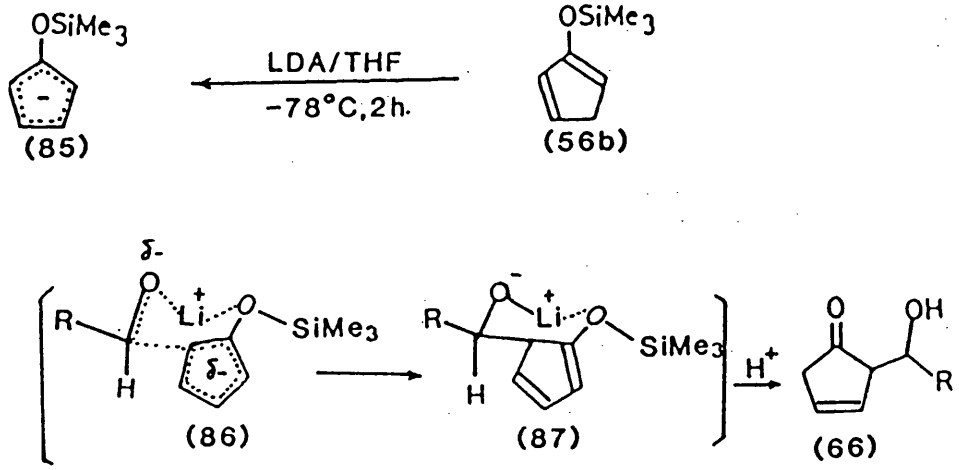
Since C(5)-H of (78) is very acidic and also because of the stabilizing intramolecular hydrogen bonding, it tends to be in its enol form (82) and also because the C(5) carbanion from the enolate (83) is "too soft" to react with the reagent (80), the carboxylation reaction can only happen at oxygen. Further more, (74) is relatively sterically crowded and (83) is further stabilized by its resonance form (84). Consequently, no further effort was devoted to this particular study.

3-4. Attempted deconjugation via the enolsilane carbanion

Assuming that the dianion (71) might be too reactive to be used for the direct aldol reaction since disubstitution by the aldehyde might occur, some other form of the dianion was sought where control might be exercised over its second potential anionic reaction.

The enol silane carbanion (85) seemed to satisfy the above requirement. It has the same potential as (71) as a dianion and can only react with one molecule of aldehyde as a mono-anion, at -78^0C in THF, retaining the silyl group. Based on this strategy, the following reaction was proposed: (Scheme 52).

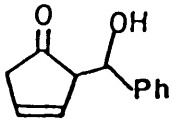
Scheme 52



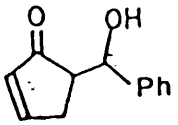
The reactions were examined with several aldehydes, quenched with NH_4Cl-H_2O or AcOH-THF. Some deconjugated aldols seem to have been obtained in each case. This conclusion was based

on the proton NMR spectrum of the crude products which contained resonances between 5.8-6.0ppm comparable with those expected for compound (88). These values compare with 6.2 and 7.8 ppm in the conjugated ketones.

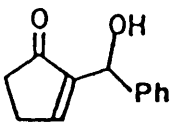
However it proved impossible to isolate compounds of the type (88) in a pure state even by short-path flash column chromatography. Instead, significantly, both the conjugated enones (89, 12%) and (90, 23%) were isolated after this purification procedure.



(88)



(89)



(90)

These observations indicate that the aldol adduct (88) can be formed using the strategy outlined in (Scheme 52), but that there is only a small activation barrier between it and its more stable conjugated isomers (89) and (90).

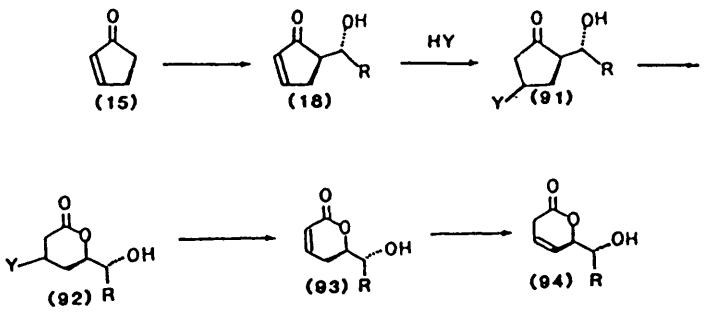
Both alumina (neutral, basic) and silica column packings were employed for chromatography and similar results were obtained in each case.

Owing to the unsolved difficulty in separation of the deconjugated aldols, no further effort was given to this aspect of the problem.

3-5. The syntheses of lactones from the aldol adducts

In view of the foregoing results for the deconjugation routes, an alternative route into six membered ring lactones was proposed as shown in Scheme 53.

Scheme 53

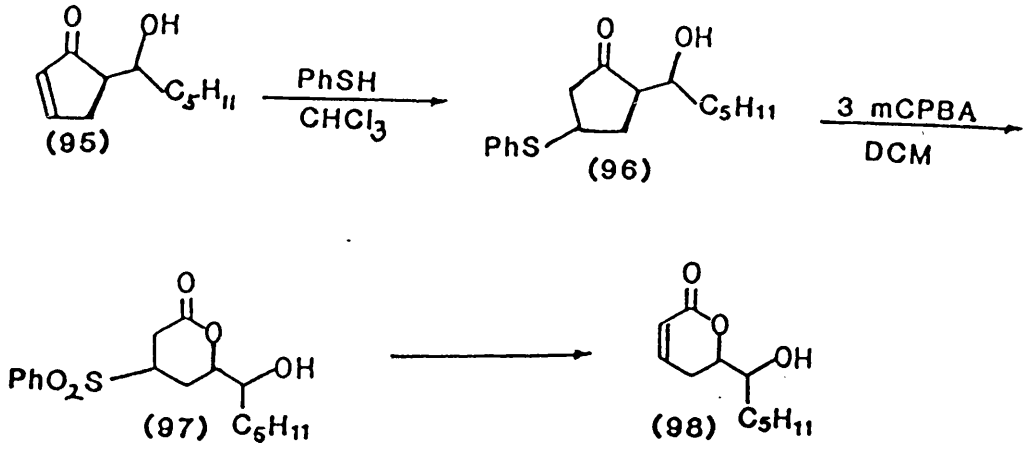


If a good leaving group could be introduced into the compound (18) to saturate the double bond, the Baeyer-Villiger oxidation of (91) should diastereoselectively produce the compound (92) which could be subsequently converted to the conjugated lactone by removing the "Y" group, and thence lead to (94).

Reaction of (18) with HBr ($HBr-H_2O-MeOH$, 0^0C to RT) did not give the desired 3-bromo-cyclopentanone aldol, substantial amounts of starting material were recovered in each case.

Thiophenol (PhSH) was utilized as an alternative reagent for this purpose[48]. It added to the double bond of 2-cyclopentenone aldol (Scheme 54)[49] smoothly, a 54% yield of yellow oil (96) as a mixture of diasteroisomers being obtained after short-path flash chromatography (silica gel).

Scheme 54



The 4-phenyl sulphonyl lactone (97) was obtained in a 17% yield by treating (96) with 3 equivalents of mCPBA[50, 51] and it underwent elimination of benzene sulphinic acid with diazabicycloundecene (3 equiv.)[52] in 56% yield. The structure of the final product (98) was confirmed spectroscopically. The ^{1}H-NMR and ^{13}C-NMR spectra of the product were very informative. They suggested that only one diastereoisomer was present. Since only one set of resonances appeared in these spectra.The chemical shift of its carbonyl carbon (164ppm), olefinic carbons (145.5 and 121.0), olefinic proton shifts (6.96 and 6.04ppm) and its infrared spectrum , ν_{max}(C=O)1705cm^{-1}, were consistent with that for a six rather than a five-membered unconjugated lactone and its mass spectrum (M^{+}=198) confirmed the structure (98).

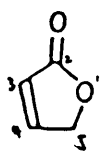
Chapter Four: The regio and diastereoselectivity of the aldol reactions between butenolide and aldehydes

4-1. Objective

Substituted butenolides have been frequently encountered as natural products. Although uses of α,β-unsaturated or β,γ-unsaturated butenolides as useful synthetic units is well documented[53] and some recent synthetic methods have been reported[54-59], no systematic study of their regio and diastereoselective functionalization has been described in the chemical literature. To fill this gap in the literature, a parallel study to that described in Chapter 2 was undertaken for the aldol reactions of butenolide.

4-2. Preparation of butenolide (99) and 2-trimethylsilyl-oxyfuran (101)

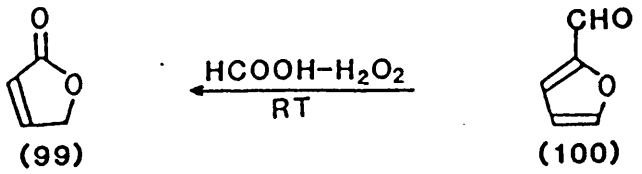
Since the butenolide (99) was not commercially available, it was necessary to prepare it.



(99)

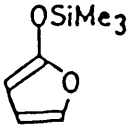
The compound (99) was obtained from furfural (100)(Scheme 55) via Baeyer-Villiger oxidation[60] and the desired compound (99) was obtained in over 54% yield.

Scheme 55



(99) (100)

Since all attempted aldol reactions between the anion of (99) and aldehydes using LDA as base[53] generated multi-component mixtures, and no aldol product could be isolated, attention was shifted to 2-trimethylsilyloxyfuran (101) as the anion equivalent.



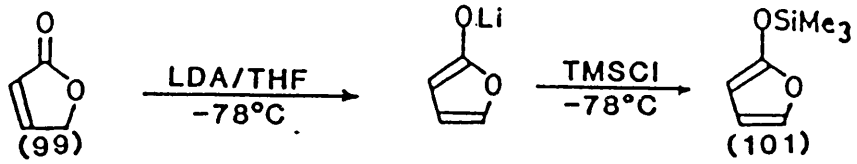
(101)

The compound (101) is a very useful reagent[53b, 61] which can undergo aldol (note: the implication here that some aldol reactions of (101) have already been studied by others)[54 - 59], Diels-Alder or alkylation reactions to give many interesting compounds.

The preparation of (101) was achieved by generating its anion with LDA in THF or sodium hydride in DMF followed by quenching with TMSCl. Better than these is the direct preparation using

$NEt_3/TMSCl$[59] as reagents as shown in Scheme 56.

Scheme 56



(99) $\xrightarrow[0°C]{NaH/DMF}$ $\xrightarrow[0°C]{TMSCl}$ (101)

(99) $\xrightarrow[0°C \rightarrow RT]{NEt_3 - Me_3SiCl}$ (101)

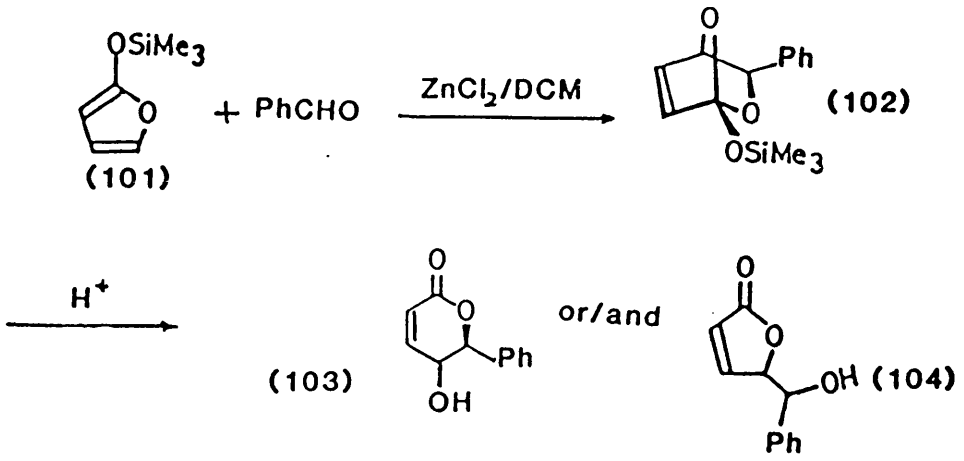
Due to its sensitivity to moisture and instability on storage at room temperature, it is necessary to use (101) soon after making it.

4-3. Lewis acid mediated reactions between (101) and aldehydes

4-3-1. Initial experiment

The first experiment using reagent (101) and benzaldehyde was performed using $ZnCl_2$ as mild Lewis acid. It was thought by one of us on the basis of related Diels-Alder reactions performed by Danishefsky[62a] that the reaction might go as indicated in (Scheme 57).

Scheme 57



That is, that the reaction might undergo a heterocyclic Diels-Alder addition to give an intermediate (102) which would undergo subsequently a ring opening promoted by nucleophilic attack at silicon to generate either (103) or (104).

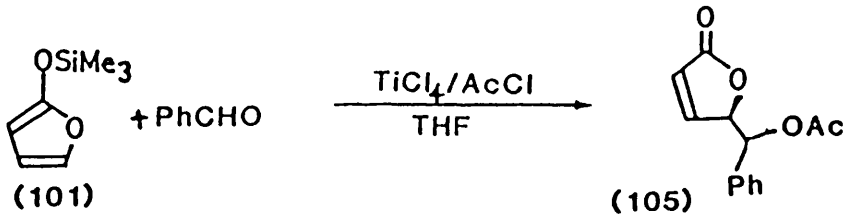
It was expected that the infrared spectrum might be the best tool for distinguishing between the two possible products (103) and (104) since they would have very similar NMR and mass spectra.

The product, a pair of diastereoisomers, from short path (silica gel) chromatography, of the above reaction had ν_{max}(C=O) 1745 cm^{-1}(neat film) which lies between ν_{max} 1760cm^{-1}, the normal frequency for a five-membered ring, conjugated lactone and ν_{max} 1730cm^{-1} that for a six-membered ring, conjugated lactone.

4-3-2. Confirmation of the structure of the reaction product

Initially, it was suspected that the reaction product was the δ-lactone since the carbonyl stretching frequency is quite different from a known γ-lactone[58] (105) ($1765cm^{-1}$) which was prepared by Japaneses workers as in Scheme 58.

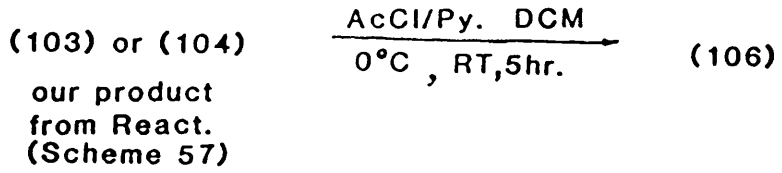
Scheme 58



(101) (105)

In order to obtain a reliable comparison with the acetate of our compound (106)(Scheme 59), the literature method for compound (105) was followed.

Scheme 59

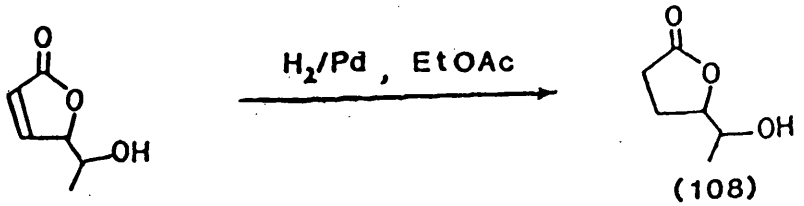


Surprisingly, the products (105) and (106) from the two separate routes were found to have exactly the same proton NMR and IR spectral data. The carbonyl stretching frequency ($1755cm^{-1}$) was different from the value appearing in the literature[58].

This discrepancy made us suspect that there was some difference in the conditions under which the IR spectra were measured. Consequently, the infrared measurement of (106) was carried out in DCM solution, and a ν_{max} value of 1765 cm^{-1} was obtained rather than 1755cm^{-1} for the liquid film. This result suggested that our product was (104).

Some support for the contention that our product was five-membered-lactone, came from the carbonyl absorption observed at 1760cm^{-1} for the saturated lactone (108) formed as in Scheme 60.

Scheme 60



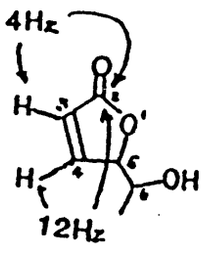
(107) (108)

The value of 1770cm^{-1} was expected for the 5-membered -lactone and ν_{max}(C=O) 1730cm^{-1} was expected for the 6 -membered-lactone.

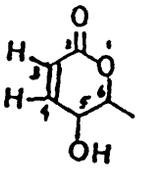
Since the product (108) was found to have the absorption of ν_{max}(C=O) 1760cm^{-1} (neat film) and 1770cm^{-1}($CHCl_3$), it is confirmed that the products from our reaction are unsaturated five-membered lactones.

Further evidance to help the confirmation of the structure was

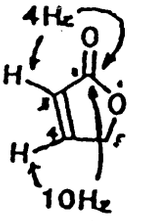
obtained by comparison of the coupling constants of our product with its possible parent lactones (99), and (110) by ^{13}C-NMR.



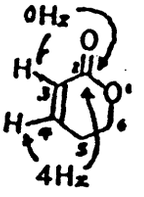
(107)



(109)



(99)



(110)

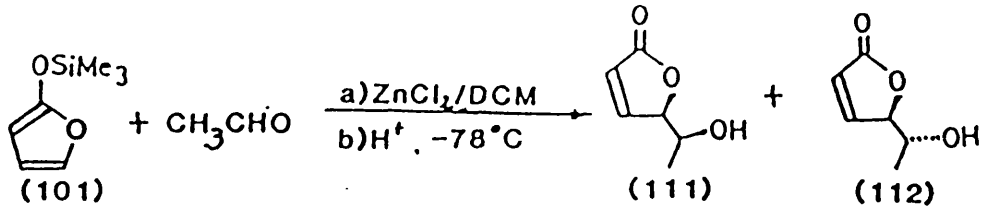
The parent lactones (99) and (110) show a ^{4}J coupling for $^{1}H(4)-^{13}C=O$ of 10Hz and 4Hz respectively and ^{3}J coupling for $^{1}H(3)-^{13}C=O$ of about 4Hz and 0Hz. Since the lowfield carbonyl-carbon of the reaction product had the appearance of a doublet of doublets with coupling constants 4 and 12Hz the structure (107) is secured.

4-3-3. The assignment of the threo and erythro isomers

The second more difficult problem concerned distinction between threo and erythro isomers.

In order to distinguish the two diastereoisomers, isolation of pure samples of each isomer was necessary. The separation of these two isomers was extremely difficult. i.e. the reaction as cited in Scheme 61 gave a pair of diastereoisomers in the ratio of 21:79. Eventually, the right HPLC conditions were

Scheme 61



found (still there is some overlap between these two isomer in EA/hexane=1:1) which required two weeks of chromatographic effort to isolate 200 mg of each isomer in a pure state. Since they had very similar spectroscopic data, it was too difficult to assign their stereochemistries from ordinary ^{1}H-NMR spectra.

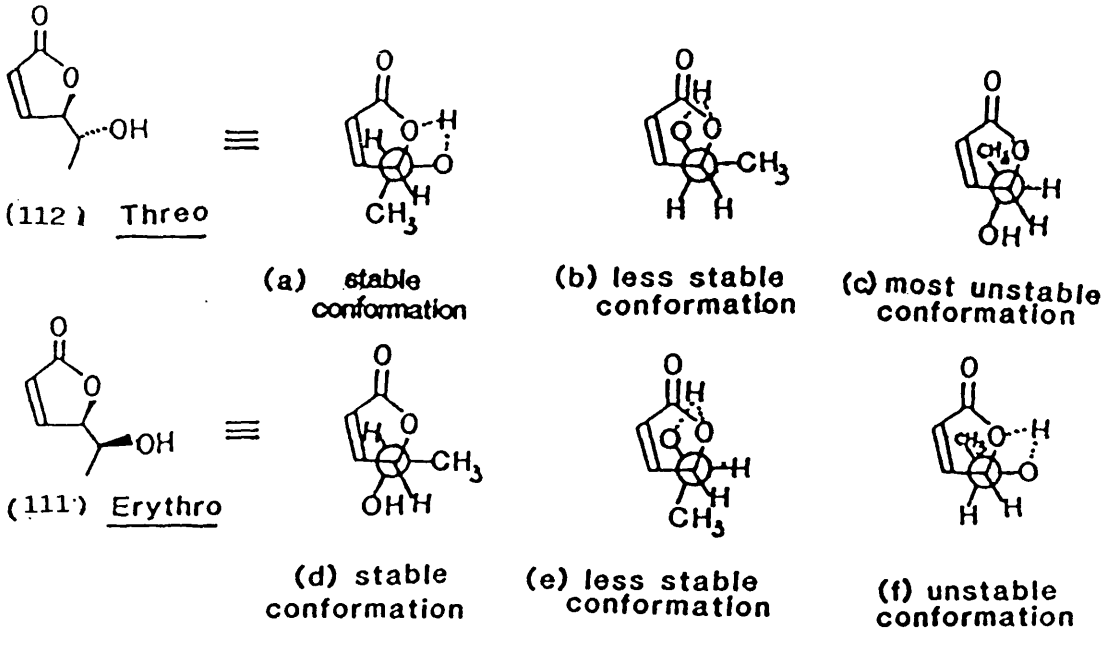
4-3-3-1. Conformational analysis of each isomer

The preferred conformations of both of the isomers (111) and (112) arose from analyses, which are illustrated in (Scheme 62).

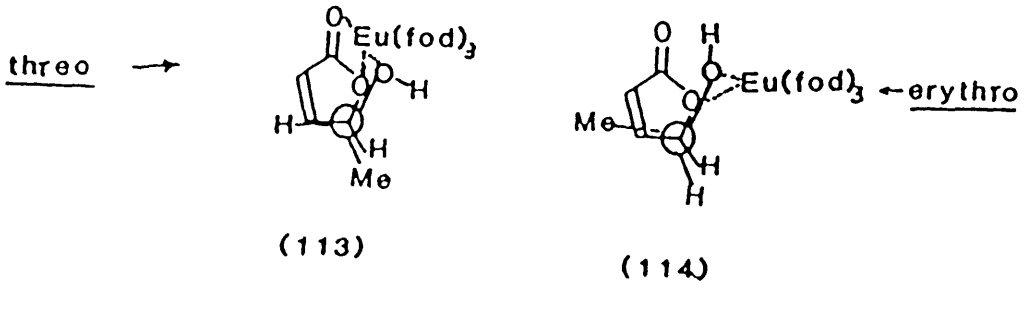
Firstly, since (a) is the most stable conformation for threo isomer (112), the intramolecular hydrogen bonding should be readily recognized and its broad absorption of OH in its infrared spectrum wouldn't change when the solution of the sample was diluted. But in contrast, (d) is the favourable conformation for the erythro isomer (111), thus, there would be less intramolecular hydrogen bonding in this instance

instead, the intermolecular hydrogen bonding should be dominant which should be observable from infrared experiment.

Scheme 62



Secondly, if some lanthanide shift reagent was added into the sample, the free rotation between C(5)-C(6) would be blocked due to chelation between the metal and the two oxygen atoms. In the threo isomer (112), the chelate (113) would be formed which is more stable than the chelate (114) formed by the erythro isomer. The latter having more eclipsing interaction (more torsional strains).



The δ_{Me} of the erythro isomer is expected to be less affected than the threo.

Accordingly, two experiments were performed on the diastereoisomers cited in (Scheme 61). First is the infrared measurement of each of the isomers in different concentrations of CCl_4; the second is the $Eu(fod)_3$ ^1H-NMR study of each of the isomers.

4-3-3-2. The infrared experiments

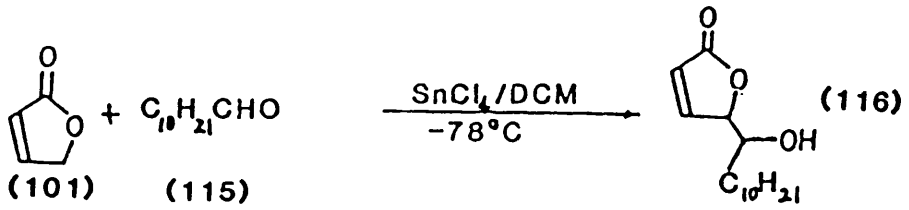
In the infrared experiment, when solutions of the samples were fairly concentrated, both the major and the minor isomer have very broad absorptions (γ_{max}(OH) 3450-3560 cm^{-1}).

Even though the solution of the major isomer was diluted several times, no change could be observed in its hydroxyl infrared absorption. In the case of the minor isomer, although, the change of the infrared absorption of the OH group in different concentrations is not dramatic, the shape of the OH peak clearly becomes sharper and sharper and the absorption reaches 3600 cm^{-1} in very dilute solution.

This result is in agreement with our expection and it suggests that the major isomer of our product is threo and the minor one is the erythro.

In order to confirm that the threo isomer is generally the major isomer, the compound (116) was chosen for the same infrared measurement. The compound was made from the reaction in Scheme 63.

Scheme 63



Only one isomer of (116) was obtained from this reaction and it was assumed to be the threo isomer since its infrared absorption intensity (γ_{max}(OH)=3620-3480 cm^{-1}(br.)) showed no change in various concentrations solution (CCl_4).

4-3-3-3. The lanthanide NMR study

The 270MHz ^{1}H-NMR spectra were obtained on 270MHz proton NMR spectra were taken on pure samples of the two diastereoisomers of similar concentrations in $CDCl_3$ and their solution containing 0.12, 0.24 and 0.36 molar concentrations of Eu(fod)$_3$ (an approximately 20/80 mixture of the two diastereoisomers in $CDCl_3$ and on their solution). The results are collected into Table XIII

Table XII

The chemical shift (ppm) of isomers (113)(114) under different concentrations of $Eu(fod)_3$

No	The concentration of $Eu(fod)_3$ (M)	The chemical shift (ppm)	
		Major isomer	Minor isomer
1	0	7.48, 6.20, 4.95, 3.95, 1.32	7.58, 6.20, 4.95, 4.07, 1.325
2	0.065	7.84, 6.55, 5.55, 4.80, 1.80	7.93, 6.55, 5.80, 5.10, 1.95
3	0.141	8.26, 7.01, 6.26, 5.75, 2.35	8.31, 6.97, 6.81, 6.25, 2.63
4	0.220	8.65, 7.45, 6.95, 6.73, 2.90	8.65, 7.35, 7.80, 7.30, 2.30

For each isomer very strong deshielding of the ether, 4.95 ppm, and carbinol methine, 3.95 and 4.07ppm, protons is apparent, stronger than any other hydrogen. This suggest bidentate ligation of the aldols via the alcoholic and etheral oxygens to the europium atom giving structures analogous to conformations (113) and (114).

Presumably, the steric crowding between the methyl group and the alkyl groups of $Eu(fod)_3$ would result in $Eu(fod)_3$ being slightly futher apart from the methyl group in the five membered, metal-containing ring of the chelate and this would make the ring of the chelate slightly bent. In the threo case, if the $Eu(fod)_3$ are slightly bent to the butenolide ring, the two methines on the both side of the chelate will not be equidistant from the the metal, therefore their shifts should be quite different. In contrast, for the erythro case, because of the two methine protons on the same side of the ring of chelate even though the ring might be slightly bent, the shifts on the two methine protons should be quite similar since they remain nearly equidistant from the metal.

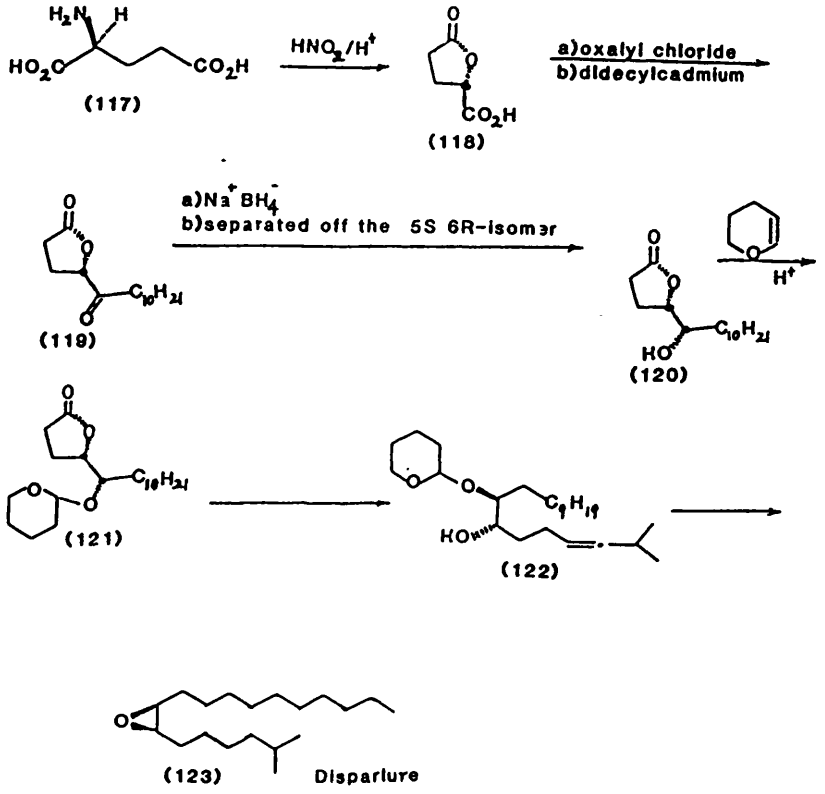
From the Table XIII, it can be seen that for one isomer the methyl groups have very similar (0.98-1.02) shifts, this must be the erythro isomer, and for the other a greater difference (0.65, 1.02) in shifts is seen and this must be the threo isomer. Further support for our assignment was obtained from the following synthetic correlation.

4-3-3-4. via conversion to known compound

Marumo et al. have synthesized the natural product disparlure (the sex attractant emitted by the female gypsy moth) from

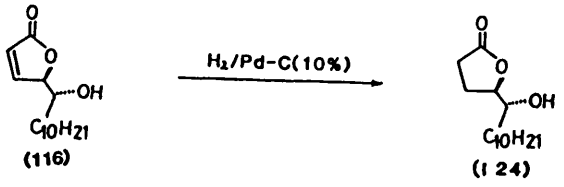
aspartic acid[62](117) as shown in Scheme 64. One of the intermediates is the threo isomer of the γ-substituted butanolide (120).

Scheme 64



In order to correlate our compound with (120), it was hydrogenated (Scheme 65).

Scheme 65



The product (124) obtained from the above reaction had exactly the same chemical shifts and J values as quoted for compound (120). Thus the compound (116) was finally and conclusively confirmed as the threo isomer.

4-4. Mechanistic study of reactions between silyloxyfuran (101) and aldehydes mediated by various Lewis acids

4-4-1. Some questions regarding the mechanism of the reaction

The following questions concerning these reactions needed to be addressed:

(a) Do they proceed via a Diels-Alder intermediate through a ring, metal-chelated transition state?[65]

(b) If the reaction proceeds via a Diels-Alder adduct, why is the five-membered lactone the sole reaction product?

(c) Regioselectivity. If the reaction proceeds via the aldol route, why is no α-substituted aldol product detected? Our previous findings indicate that Lewis acid mediated aldol reactions always react via Zimmerman cyclic six centered transition state to give α-substituted aldols.

(d) How can we account for the diastereoselectivity observed?

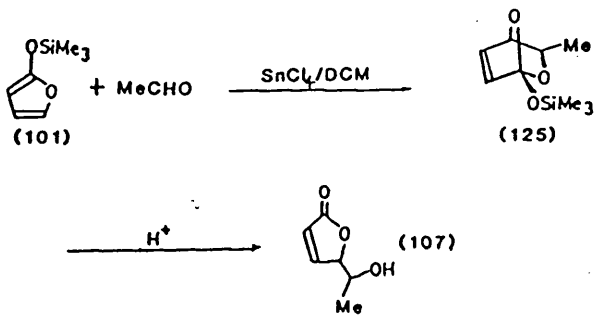
4-4-2. The NMR experiment

Attempts were made to observe the putative cycloadduct by conducting the proposed reaction shown in Scheme 66, in an NMR tube whilst observing changes in the spectrum. The intermediate (125) would show different chemical shifts for

the two vinyl protons(=C(2)-H and =C(3)-H) in (125) which might be expected to appear between 5.0-5.6 ppm and which might be detected by low temperature ^{1}H-NMR. (Scheme 66).

Four spectra were recorded after different reaction times and at different reaction temperatures: a) The reactants at -78^{0}C; b) at -78^{0}C, 10 minutes after the addition of Lewis acid; c) After 0.5 hours at -78^{0}C and 5 minutes at -40

Scheme 66



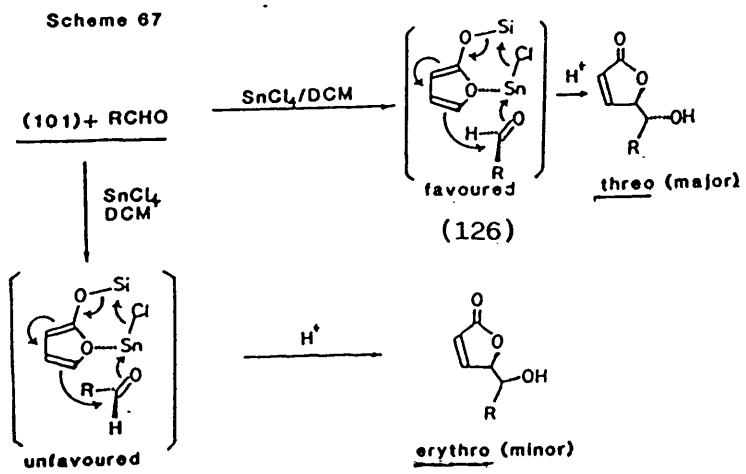
^{0}C; d) After a further 20 minutes -20^{0}C. The data obtained from the ^{1}H-NMR spectra from the above experiment indicated that the reaction proceeded very slowly at -78^{0}C, and was getting faster at higher temperature. But other than the final product (5-substituted butenolide), no intermediate (as indicated by the appearance of the resonances between 5.0-5.6ppm) could be detected

These observations suggest either that an aldol mechanism operates here or that the cycloadduct concentration does not build up to the levels detectable by NMR at 270MHz.

4-4-3. A proposal for a tricyclic chelated transition state

In order to explain why our aldol addition only occurs at the γ-position of (101), a new transition state (tricyclic transition state) is proposed as follows (Scheme 67):

Scheme 67



Because the transition state (126) is more stable than that of (127), the threo isomer should be formed faster, especially when R is a sterically demanding group. This idea is supported by the data listed in (Table XIV):

This tricyclic-transition state not only explains why the reaction is regioselective but also explains its diastereoselection.

As an application of our method, a natural product[66] (141) was obtained by hydrogenation (Pd-C, H_2) of aldol (139) in quantitive yield[67]. Our effort was also extended to the synthesis of compound (142), by treating (136) with

Table XIV

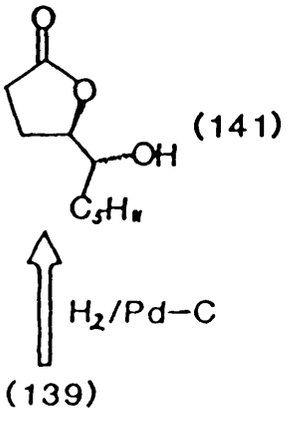
The aldol reaction of (101) with aldehydes mediated by $SnCl_4$ under the condition (DCM, -78°C, 1 hr.)

Aldehyde	The product of the reaction		
	No.	Yield[a] (%)	Ratio[b] of (T-)/(E-)
MeCHO	(136)	>95	87 : 13
EtCHO	(137)	73	81 : 19
PhCHO	(138)	80	88 : 12
$C_{10}H_{21}CHO$	(116)	86	>98 : <2
$C_5H_{11}CHO$	(139)	77	93 : 7
i-PrCHO	(140)	91	94 : 6

a. the yield is the overall yield from furanone (99) and corrected from the recovery of starting (99).

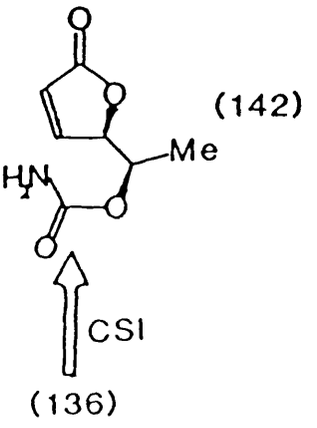
b. the ratio was determined via GLC analysis.

CSI (chlorosulfonyl isocyanate), which is a very useful precursor for stereocontrolled syntheses of some natural amino sugars.



(141)

(139)



(142)

(136)

4-5. Diastereoselection study of the aldol reaction between (101) and aldehydes mediated by different Lewis acids

A range of Lewis acids as well as one Lewis base have been examined with a view to finding a better catalyst for our directed aldol reaction, for the reaction of silyloxyfuran (101) and acetaldehyde (Scheme 68). The results are listed in Table XV.

Scheme 68

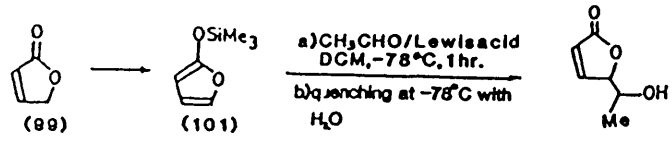


Table XV

The Diastereoselection of the reaction(Scheme 68)

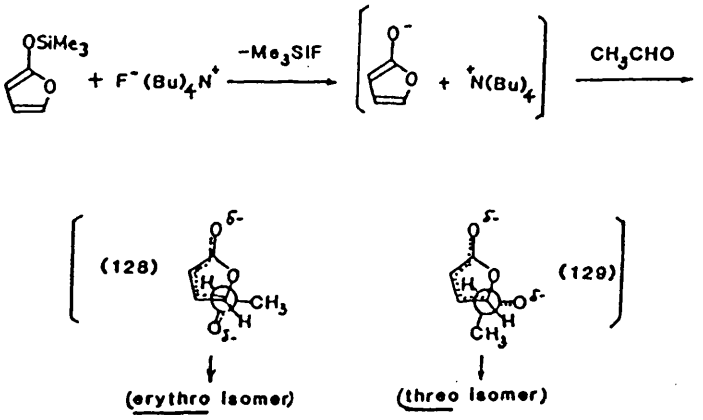
No.	Lewis acid	Aldol product	
		Yield[a](%)	Ratio[b] of (T-)/(E-)
1	$TiCl_4$	94	63 : 37
2	$Ti(O\text{-}i\text{-}Pr)_4$	52	75 : 25
3	BF_3	85	69 : 31
4	BCl_3	65	76 : 24
5	$AlCl_3$	95	86 : 14
6	$SnCl_4$	>95	87 : 13
7	$ZnCl_2$	93	79 : 21
8	ZnI_2	trace	
9	TBAF	71	42 : 58
10	TMS-triflate	94	89 : 11

a. the yield is the overall yield from butenolide and is corrected for the recovery of (99) and determined via internal standard GLC analysis.

b. ratio determined via GLC analysis.

The results in Table XV indicate that most of the Lewis acids examined here can mediate the above aldol reaction (Scheme 68) with the same regio and diastereoselectivity, but that $SnCl_4$ is superior to the others with regard to both chemical yield and diastereoselection.

Scheme 69



Poor diastereoselection is achieved in the aldol reaction mediated by the Lewis base(TBAF). The reason is illustrated in (Scheme 69). It can be argued that a "naked" carbanion is formed during the reaction and an "open" transition state leads to most of the erythro aldol diastereoisomer.

The difference in energy between (128) and (129) would be very small because even though the dipole-dipole repulsion between the two oxygens is possibly present, it might be very small

and the methyl group is the most important sterically demanding group which controls the favourable conformation of the transition state under the reaction conditions. Thus, the reaction showed only slightly an erythro selection (T-/E-=42:58).

Table XVI*

The diastereoselection of the aldol reaction between (101) and MeCHO under various conditions

reaction condition				Aldol product (136)	
Catalyst	Solvent	Time (min)	T (^{o}C)	Yield(Conversion) (%)[a]	Ratio[b] of T-/E-
$ZnCl_2$	THF	24hr.	-15 to RT	94 (80)	86 : 14
$ZnCl_2$	DCM	60	-78	93 (72)	79 : 21
$SnCl_4$	DCM	60	-78	>95 (67)	87 : 13
$SnCl_4$	THF	8hr.	-78	>95 (94)	88 : 12
$SnCl_4$	THF	60	-78	91 (74)	81 : 19
$SnCl_4$	THF	4days	-60 to-40	95 (64)	83 : 17
$SnCl_4$	ether	8hr.	-78	91 (53)	80 : 20
$SnCl_4$	DCM	10	-78	93 (70)	82 : 18

* all reactions indicated here were only performed once and ratios were calculated by internal standard GLC analysis.

a. the yields here were the overall yields from butenolide and corrected for the recovery of (99). The conversion here is the yield before correction determined via internal standard GLC analysis.

b. ratio determined via GLC analysis.

The effects of altering other reaction parameters with the objective of improving diastereoselectivity are summarized in Table XV. Although not clear cut, some trends are nevertheless visible in the data collected in Table XVI.

Firstly, THF is the solvent of choice with regard to both diastereoselection and yield. But, it is necessary to point out that the conditions for using THF are very demanding as it is very hygroscopic and it must be vigorously dried and kept under dry argon, or the reaction yield falls sharply.

Secondly, the longer reaction time seems to improve threo selection. The slightly better threo selection observed in entry 3 might be caused by the equilibration between the threo and erythro isomer since the threo aldol is the more stable one under equilibration conditions.

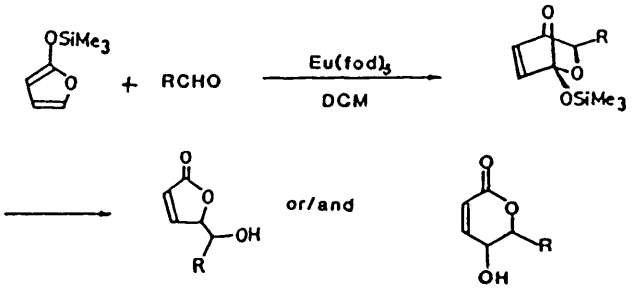
4-6 The aldol reactions of (101) and aldehydes mediated by lanthanide reagents.

Besides being extremely important tools for NMR studies, lanthanides have drawn increasing attention[64] during the last decade as catalysts in organic synthesis

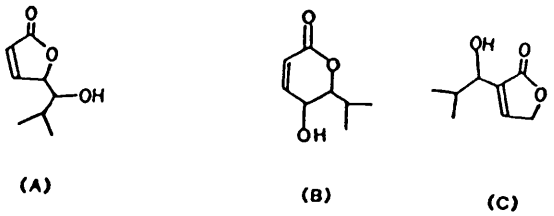
The lanthanide shift reagent [$Eu(fod)_3$] was found to be a

good catalyst for hetero Diels-Alder reactions[65]. Since we believed that a Diels-Alder cycloadduct might be an intermediate in our aldol reaction, it was of interest to examine any catalytic activity, the reagent might possess for the reaction in Scheme70. Either 5- or 6-membered lactones might be formed. No literature reports could be found regarding the use of lanthanide reagents as catalysts in aldol reactions.

Scheme 70



Surprisingly, the sole product isolated was neither of the 5- or 6-membered-ring lactones expected as in the case of reaction of (101) with 2-methylpropanal, even though the infrared, ν_{max}(OH) 3450cm^{-1}(neat film), and mass spectral data, M+1(C.I.)=157(100), are consistent with any of the structures A,B or C,



(A) (B) (C)

(A) and (B) were excluded however because only one vinyl proton (δ 7.38 ppm) appears in its ^{1}H-NMR spectrum.

This result suggests that the reaction proceeds not via a Diels-Alder mechanism, but more likely via a metal trapped regio-selective aldol reaction.

No literature precedent exists for the discovery that lanthanides can mediate aldol reactions. The reason why their behaviour differs from Lewis acids as regards regio-selection of C-3 instead of C-5 still remains unclear. Several aldehydes have been subjected to $Eu(fod)_3$ catalysis in the aldol reactions indicated in (Scheme 71). All of them give the C-3 aldol products rather than C-5 substituted products (Table XVII).

Scheme 71

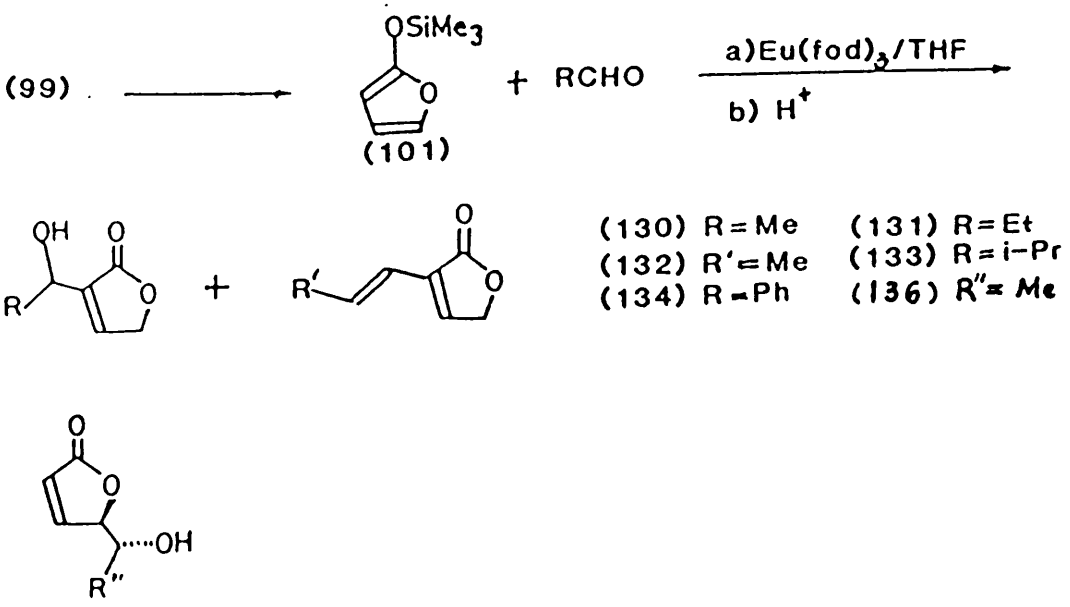


Table XVII

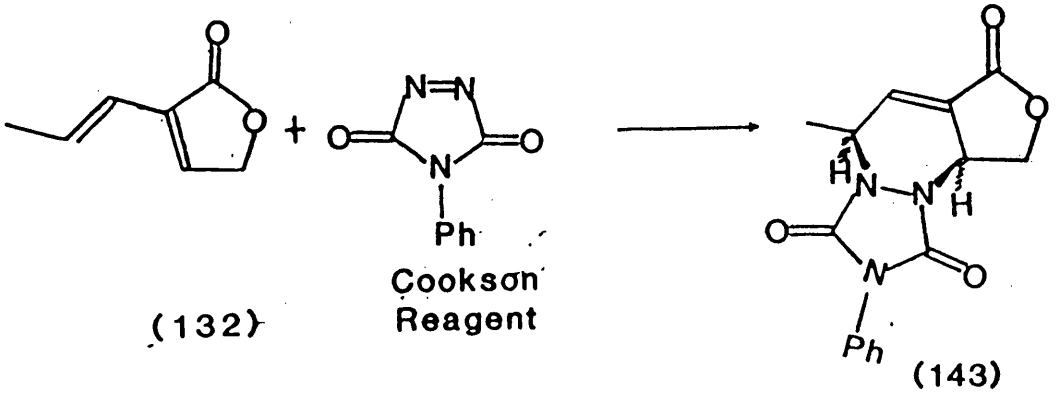
The aldol reaction catalyzed by lanthanide reagent

No.	Reaction condition			Product	By-product
	lanthanide reagent	Temperature (^{o}C)	Time (day)	yield (%)[a]	yield (%)[a]
1	$Pr(fod)_3$	RT	7	(130)(56%)	(136)(14%)
2	$Eu(fod)_3$	RT	7	(130)(68%)	b
3	$Eu(fod)_3$	67	2	(134)(73%)	b
4	$Eu(fod)_3$	40	3	(131)(54%)	(132)(21%)[c]
5	$Eu(fod)_3$	60	2	(133)(65%)	b

a. the yields were corrected by the recovery of butenolide determined by an internal standard GLC analysis.

b. multi-component by product were unidentified, no γ-aldol were detected by GLC analysis of crude product.

c. the structure of compound (132) was confirmed by a Diels-Alder reaction of (132) with Cookson's reagent[68] in which the new heterocyclic compound (143) was obtained.



Since the $Pr(fod)_3$ reagent responds differently to $Eu(fod)_3$ in NMR measurements, it was of interest to see whether or not there is some difference between them in mediating aldol reactions.

One experiment was performed based on this idea and the result in (Table XVII) shows that $Pr(fod)_3$ acts in a very similar manner to $Eu(fod)_3$ to generate the C-3 aldol, but it is not as efficient as $Eu(fod)_3$ as a regiospecific catalyst since some C-5 aldol product was also detected from the reaction.

The products obtained in this section are confirmed by full spectroscopic data as well as by reference to our previous products (see experimental part).

EXPERIMENTAL FOR

PART ONE

<< EXPERIMENTAL >>

SOLVENTS, REAGENTS AND EXPERIMENTAL:

Solvents were distilled and dried, prior to use, by standard methods. Reactions involving moisture sensitive materials were carried out under an inert atmosphere of dry nitrogen or argon. All evaporations were carried out *in vacuo* via rotary evaporator below 50°C and all liquid/liquid extractions were carried out as follows unless otherwise stated: "The product was extracted with organic solvents (ether or ethyl acetate) five times and the combined organic phase was washed several times with brine or saturated ammonium chloride solution, dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*."

Most chemicals used as starting materials were commercially available, and all were checked or further purified (distilled or recrystallized) before use. Other derivatives were prepared by literature methods as cited. All new reactions were followed by either TLC, GLC or UV / IR .

CHROMATOGRAPHY

TLC was carried out using commercially available pre-coated silica gel 60 F_{254}. Visualizations were achieved by ultraviolet fluorescence at 254 nm and / or the following

spray reagents:

(a) Iodine vapour

(b) 0.5% a aqueous potassium permangnate solution

(c) 5.0% ethanolic solution of anisaldehyde with concentrated sulphuric acid (1%)

(d) 7% methanolic solution of phosphomolybdic acid (PMA)

Medium pressure column chromatography was carried out using silica gel (Merck 7747) and for flash column , using silica gel (Merck 9385). Preparative TLC was carried out using commercially available (2mm or 4mm thick) pre-coated silica gel 60 F_{254} silica plates with concentration-zone. All determinations of the ratio of diastereoisomers were carried out using temperature programmed GLC by measuring the area of each peak. Some extremely difficult separations were carried out by using HPLC .

SPECTROSCOPY

Nuclear magnetic resonance (NMR) spectra were recorded at 270 MHz (^{1}H) or 67.5 MHz (^{13}C) unless stated otherwise. All spectra were run in deuterochloroform ($CDCl_3$) or deuterium oxide (D_2O) with tetramethylsilane (TMS) as internal standards unless specified otherwise. Chemical shifts (δ) are expressed as downfield shifts from TMS in all cases with multiplicities denoted by s(singlet), d(doublet), t(triplet), q(quartet), p(pentet), dd(doublet of doublets), or

m(multiplet) etc..

Infrared (IR) spectra were recorded as neat films with the absorption frequencies (ν) expressed in cm^{-1}.

Ultraviolet (UV) spectra were recorded as ethanolic solutions unless stated otherwise. Maximum absorptions (λ_{max}) were expressed in nm with the molar absorptivity (ε) as $10^{-2} m^2 mol^{-1}$.

Mass spectra (MS) were recorded using electron impact (EI) at 70 eV unless otherwise stated .

OTHER TECHNIQUES

All melting points are uncorrected .
Optical rotations were carried out in the cell of ($0.5\ cm^3$) and DCM solution unless stated otherwise.
Elemental analyses were done by Mr. Carver of the School of Chemistry .

INSTRUMENTATION :

IR	Perkin-Elmer 197 and 1310
UV	Perkin=Elmer 420 and Lambda 3
MS	VG 7070E with 2000 data system
MP	Electrothermal
HPLC	Gilson Model 303 / 201 / 802 + LDC / Milton

	Roy spectro Monitor III + Servogor 120 recorder
GLC	AI Model 93 Gas Chromatograph
^{1}H-NMR	Jeol GX 270 Fourier Transform Spectrometer
	EM 360 NMR spectrometer
	Hitachi Perkin-Elmer R-24B
^{13}C-NMR	Jeol GX 270 Fourier Transform Spectrometer
Optical Rotation	Perkin-Elmer 141 Polarimeter
Elemental Analyses	Carlo Erba Elemental Analyzer MOD 1106

Preparation of 2-(hydroxyphenylmethyl)-cyclopentanone (24) via Pd/C catalyzed hydrogenation of (42)

The hydrogenation was carried out (1 at., RT, 2.5 h), following the method described by Vogel and on a mixture of unsaturated aldol (42)(a pair of diastereoisomers, 0.28g, 1.5mmol) using 10% Pd on C (30mg) in EtOAc(15ml). The catalyst was removed after reaction by filtration through celite, washed thoroughly with EtOAc(dry) and the solution was concentrated under vacuum. The desired compound was obtained (0.28g, >98%) as a pale yellow oil and the major isomer of it was confirmed as the threo isomer by a comparison with data for a known compound [32].

IR ν_{max} 3460(OH), 1725(C=O) cm^{-1}

^{1}H-NMR (mixture of diastereoisomers):

Threo isomer: δ 7.20(5H, s, C-H of Ph), 4.68(1H, d, J= 9Hz, O-CH-), 4.47(1H, s, OH), 1.28-2.54(7H, br.s, aliphatic CH).

Erythro isomer: δ 7.20(5H, s, C-H of Ph), 5.16(1H, d, J=2.0Hz, O-CH-), 3.90(1H, s, OH), 1.14-2.44(7H, br.s, aliphatic CH).

Preparation of 2-(1'-hydroxy-2'-phenylethyl)-cyclopentanone (25) via hydrogenation of (43)

Applying the same experimental procedure as that for the preparation of (24) and starting with (43)(0.31g, 1.53mmol)

and 10% Pd on C(35mg) in EtOAc(15ml), the desired compound (25)(0.31g,>98%) was obtained as a pale yellow oil. The major isomer of the product was confirmed as the threo isomer by comparison with literature data[32].

IR: ν_{max} 3420, 3390(OH), 1720 cm^{-1}

^{1}H-NMR (mixture of diastereoisomers):

Threo isomer: δ 7.30(5H, s, CH of Ph), 4.36(1H, t, J=8Hz, O-CH-), 2.78(2H, d, J=8Hz, CH_2 of Bz), 2.71(1H,s,OH), 1.70-1.28(7H, br.s, aliphatic CH).

Erythro isomer: δ 7.31(5H,s, CH of Ph), 3.85(1H, q, J=6Hz, O-CH-), 3.64(1H, s, OH), 1.30-2.89(9H, broad, aliphatic CH).

Preparation of 2-(1´-hydroxylundecyl)-cyclopentanone (29) via catalytic hydrogenation of (44)

Applying the same experimental procedure as that described for the preparation of (24) and starting from unsaturated aldol (44)(single isomer, 0.45g, 1.78mmol), the desired (29) (0.42g, 93%) was obtained as a pale yellow oil and confirmed initially as threo by referring to the assignment of (24) and (25).

IR: ν_{max} 3510(OH), 1710(C=O) cm^{-1}.

^{1}H-NMR:

δ 4.12(1H, br.s, OH), 3.69(1H, br.t, J=6.5Hz, C-1´), 2.38(1H, m, C-2), 2.25-1.98(3H, m, $C\text{-}3_A$ and C-5), 1.79(1H, m, $C\text{-}3_B$), 1.39-1.60(4H, m, C-4 and C-2´), 1.28(16H, br.s,

C-3′ to C-10′), 0.89(3H, t, J=7Hz, C-11′).

^{13}C-NMR:

δ 223.9(C-1), 72.1(C-1′), 53.8(C-2), 38.4(C-5), 35.1(C-2′), 31.8(C-3′), 29.6(C-4′), 29.5(C-5′ to C-7′), 29.3 (C-8′), 26.7(C-3), 24.7(C-9′), 22.6(C-10′), 20.5(C-4), 14.1 (C-11′).

MS (C.I.): 255$(M+1)^+$, 237$(M+1-H_2O)^+$, 113, 84.

Preparation of racemic threo-7-hydroxy-6-hexadecanolide(30) via Baeyer-Villiger oxidation of (29)

To a solution of compound (29)(0.121g, 0.48mmol) in DCM (8ml) was added powdered sodium bicarbonate (75mg, 0.9mmol) followed by addition of mCPBA(0.9mmol) at 0^{o}C. The resulting mixture was stirred (RT, 3.5h) and the reaction was followed by TLC (silica gel, EtOAc/pet. ether=1:2). After addition of a saturated solution of $NaHCO_3$ and usual work-up, the desired compound (30)(m.p. 52.5^{0}C, 168mg, 91%) was obtained as a pale yellow oil and confirmed from following data:

IR: ν_{max} 3570(s), 3550-3400(br.s, OH), 1715(C=O) cm^{-1}.

^{1}H-NMR:

δ 4.20(1H, dt, J=11 and 4.5Hz, C-6), 3.57(1H,m, C-7), 2.60-3.20(1H, br.s, OH), 2.55-2.68(1H, ddd, J=17.0, 10.0 and 7Hz), 1.70-2.04(3H, m, cyclic aliphatic CH), 1.44-1.60(2H, br.s, aliphatic CH), 1.26(16H, br.s, aliphatic CH), 0.88(3H,

t, J=7Hz, Me).

MS (C.I.): 271$(M+1)^+$, 253$(M+1-H_2O)^+$.

Elemental analysis: Found: C 71.0%; H 11.2%.

Calculated for $C_{16}H_{30}O_3$ C 71.0%; H 11.1%.

Aldol reaction of cyclopent-2-enone with aldehydes under base conditions

Method A: Using LDA as base

To a solution of lithium diisopropylamide (LDA, freshly made from diisopropylamine and n-BuLi at 0°C, 5.5mmol) in THF(15ml), was added dropwise a solution of cyclopent-2-enone (5mmol) in THF(5ml) at -78°C under an atmosphere of nitrogen with stirring. The resulting mixture was stirred (10 min), a solution of aldehyde (5mmol) in THF (5ml) was then introduced dropwise, stirred (-78°C, 25min) and quenched by addition of aqueous ammonium chloride. After being warmed to RT, the organic layer was extracted with ether (4 X 25ml), washed with brine, dried over $MgSO_4$ and concentrated in vacuo to leave an oil, which was subjected to the further purification by flash chromatography (silica gel) or to get the yield and the diastereomeric ratio of the aldols, analysed by internal-standard GLC analysis.

Method B: Using MeONa as base

To a mixture of cyclopent-2-enone (5mmol) and aldehyde (5mmol) in MeOH (5ml), was added dropwise a solution of MeONa (5.5mmol in 5.5ml of MeOH) at -78°C. The resulting mixture was stirred (-78°C,24 h) under an atmosphere of nitrogen (or argon), quenched with aqueous ammonium chloride and worked-up as normal. The products were separated by column chromatography and the chemical yields as well as the diastereomeric ratios were determined via internal-standard GLC analysis of the crude product.

Method C: Using t-BuOK as base

To a mixture of cyclopent-2-enone (5mmol) and aldehyde (5mmol) in t-BuOH (5ml), was added dropwise a solution of t-BuOK (5.4 mmol in 6ml of t-BuOH) at 0°C. The resulting mixture was stirred (0°C,2h), quenched (0°C) and worked-up as normal.

Method D: Using Et_3N as base

To a mixture of cyclopent-2-enone (5mmol) and aldehyde(5mmol) in (or without) MeOH (5ml), was added Et_3N(1 equiv. or 5ml) at RT.The resulting mixture was stirred(24h) and concentrated in vacuo to leave an oil which was further purified by flash chromatography and characterized from its spectral data. The yield and the diastereomeric ratio were determined by internal standard GLC analysis of the crude product.

Preparation of 5-(1´-hydroxypropyl)-cyclopent-2-enone(40) via Method A

Using the experimental procedure described in Method A , starting with cyclopent-2-enone (410mg, 5mmol) and propanal (290mg, 5mmol), the title compound (40)(448mg, 64%) was obtained as a pale yellow oil (a pair of diastereoisomers, threo / erythro = 76:24) and characterized as follows:

IR: ν_{max} 3450(br.s, OH), 1685(C=O), 1590(C=C), 1370cm^{-1}.

^{1}H-NMR:

Threo isomer: δ 7.78(1H, dt, J=6.0 and 2.5Hz, C-3), 6.20(1H, dt, J=6.0 and 2.0Hz, C-2), 4.20(1H, br.s, OH), 3.70 (1H, ddd, J=10.5, 4.5 and 2.0Hz, C-6), 2.94(1H, ddd, J=18.5, 7.0 and 2.5Hz, C-4$_A$), 2.70(1H, m, C-5), 2.50(1H, m, C-4$_B$), 1.38-1.90(2H, m, C-7), 0.98(3H, t, J=7Hz, C-8).

Erythro isomer: δ 7.79(1H, dt, J=6.0 and 2.5Hz, C-3), 6.25(1H, dt, J=6.0 and 2.0Hz, C-2), 4.22(1H,m, C-6), 3.32(1H, br.s, OH), 2.68-2.80(2H, m, C-4, C-5), 2.40(1H, C-4 or C-5), 1.40-1.90(2H, m, C-7), 1.04(3H, t, J=7Hz, C-8).

^{13}C-NMR:

Threo isomer: δ 212.8(C-1), 164.8(C-3), 133.4(C-2), 72.8(C-6), 48.9(C-5), 32.1(C-4), 27.2(C-7), 9.1(C-8).

Erythro isomer: δ 211.9(C-1), 165.3(C-3), 133.8(C-2), 71.1(C-6), 49.8(C-5), 30.3(C-4), 28.0(C-7), 9.3(C-8).

MS (C.I.): 141$(M + 1)^+$, 123$(M + 1 - H_2O)^+$, 83$(C_5H_6O + 1)^+$

Preparation of 5-(1′-hydroxy-2′-methylpropyl)-cyclopent-2-enone (41) via Method A

Starting with cyclopent-2-enone (410mg, 5mmol) and 2-methylpropanal (360mg, 5mmol) by method A, the desired aldol (41) was obtained (524mg, 68%) as a pale yellow oil (a pair of diastereoisomer, threo / erythro = 93 : 7) and characterized as follows:

IR: ν_{max} 3470(br.s, OH), 1690(C=O), 1585(C=C) cm^{-1}.

^{1}H-NMR:

Threo isomer: δ 7.78(1H, dt, J=6.0 and 2.5Hz, C-3), 6.18(1H, dt, J=6.0 and 2.0Hz, C-2), 4.22(1H, br.s, OH), 3.50 (1H, dd, J=9.5 and 3.0Hz, C-6), 2.84(1H, ddt, J=20.0, 7.5 and 2.0Hz, C-4_A), 2.40(1H, dq, J=20.0 and 2.0Hz, C-4_B), 2.48 (1H, ddd, J=9.5, 7.5 and 2.5Hz, C-5), 1.72(1H, septet of doublets J=7.0 and 3.0Hz, C-7), 1.02(3H, d, J=7Hz, C-8_1), 0.90(3H, d, J=7Hz, C-8_2).

^{13}C-NMR:

Threo isomer : δ 214.2(C-1), 164.8(C-3), 133.8(C-2), 47.4(C-5), 32.7(C-4), 31.6(C-7), 19.8(C-8_1), 15.2(C-8_2).

MS (C.I.): 155$(M + 1)^+$, 137$(M + 1 - H_2O)^+$, 83$(C_5H_6O + 1)^+$

An additional experiment was done using (41)(154mg, 1mmol) in THF(5ml) treated with LDA(1 equiv.) followed by GLC to determine the change of the diastereomeric ratio under different conditions and results are listed in Table VII.

Preparation of 5-(hydroxyphenylmethyl)-cyclopent-2-enone(42)

(A) Via Method A:

Starting from cyclopent-2-enone(410mg,5mmol) and benzaldehyde (530mg, 5mmol) via method A, the title compound (42) (687mg, 73%) was isolated as a pale yellow oil (a pair of diastereo-isomers, threo / erythro = 76 : 24) and characterized as follows:

IR: ν_{max} 3460(br.s, OH), 3030-3080(=C-H), 1680(C=O), 1585 (C=C) cm^{-1}.

^{1}H-NMR:

Threo isomer: δ 7.62(1H, dt, J=6.0 and 2.5Hz, C-3), 7.21(5H, m, CH of Ph), 6.14(1H, dt, J=6.0 and 2.0Hz, C-6), 4.68(1H, br.s, OH), 4.60(1H, d, J=9.5Hz, C-6), 2.66(1H, ddd, J=9.5, 7.5 and 2.5Hz, C-5), 2.44(1H, ddt, J=20.0, 7.5 and 2.5Hz, $C-4_A$), 2.21(1H, dq, J=20.0 and 2.5Hz, $C-4_B$).

Erythro isomer: δ 7.67(1H, dt, J=6.0 and 2.5Hz, C-3), 7.20(5H, m, CH of Ph), 6.10(1H, dt, J=6.0 and 2.0Hz, C-2), 5.30(1H, dd, J=4.5 and 3.0Hz, C-6), 3.16(1H, br.s, OH), 2.70 (1H, dq, J=20.0 and 2.5Hz, $C-4_A$), 2.56(1H, dt, J=7.5 and 2.5Hz, C-5), 1.34(1H, ddt, J=20.0, 7.5 and 2.5Hz, $C-4_B$).

^{13}C-NMR:

Threo isomer: δ 212.6(C-1), 165.2(C-3), 133.6(C-2), 141.3(C(1) of Ph), 128.6, 128.2, 126.9(carbons of Ph), 75.2 (C-6), 50.8(C-5), 32.6(C-4).

Erythro isomer: δ 211.0(C-1), 166.1(C-3), 133.9 (C-2), 142.6(C(1) of Ph), 128.2, 127.1, 125.3(carbons of Ph),

71.1(C-6), 52.3(C-5), 29.8(C-4).

MS(C.I.):189$(M + 1)^+$, 171$(M + 1 - H_2O)^+$, 107$(C_6H_6O)^+$,

83$(M + 1 - 107)^+$.

(B) via Method B:

This reaction was repeated on the same scale under the experimental conditions described in Method B and a multi-component mixture resulted. The major components isolated from the reaction were compound (45)(0.345g, 32%, b.p. 205°C) and (46)(0.31g, 17%, m.p. 123°C) along with the desired aldol(42)(17%, a mixture of diastereomers, threo / erythro = 4 : 1).

(C) via Method C:

This reaction was repeated on the same scale under the experimental conditions described in Method C, a multi-component mixture resulted. The major products isolated from the reaction were compound (45)(b.p. 205°C, 0.42g, 39%) and (46)(m.p. 123°C, 0.26g, 21%) along with the desired compound (42) (22%) which was a mixture of diastereoisomers in the ratio of 1 : 1.

(D) via Method D:

This reaction was repeated using the two following conditions: In the first case, Et_3N (5ml) was used for both solvent and

base. Along with the recovery of starting compound cyclopent-2-enone, the desired compound (42)(68mg, 7%, threo / erythro = 1 : 1) was isolated from the reaction mixture. In the second case, Et_3N (1 equiv.) as a base and MeOH (5ml) as a solvent were used. Along with the desired (42) (174mg, 18%, threo/erythro = 47 : 53), a new compound was isolated, as a yellow oil (235mg, 25%) and identified as (54) from the following data:

IR: ν_{max} 3450(OH), 1685(C=O) cm^{-1}

^{1}H-NMR:

δ 7.25-7.37(6H, m,CH of Ph and C-3), 5.50(1H,s, C-1´), 3.85(1H, br.s, OH), 2.54(2H, m, C-4), 2.38(2H, m, C-5).

^{13}C-NMR:

δ 209.6(C-1), 159.6(C-3), 147.8(C-2), 141.5(C(1) of Ph), 128.4(C(2) and C(6) of Ph), 127.7(C(4) of Ph), 126.3(C(3) and C(5) of Ph), 69.5(C-1´), 35.2(C-4), 26.6(C-5).

MS: m/e=188$(M)^{+\cdot}$, 170$(M - H_2O)^{+\cdot}$.

Preparation of 5-(1´-hydroxy-2´-phenylethyl)-cyclopent--2-enone (43) via Method A

Starting with cyclopent-2-enone (410mg, 5mmol) and 2-phenylethanal (600mg, 5mmol), the title compound (43)(556mg, 55%) was isolated as a pale yellow oil (a pair of diastereoisomers, threo / erythro = 84 : 16) and characterized as follows:

IR: ν_{max} 3450(br.s, OH), 3020-3060(=CH), 1690(C=O), 1595 (C=C) cm^{-1}.

^{1}H-NMR:

Threo isomer: δ 7.74(1H, dt, J=6.0 and 2.5Hz, C-3), 7.30(5H, m, CH of Ph), 6.20(1H, dt, J=6.0 and 2.0Hz, C-2), 4.03(1H, m, C-6), 3.96(1H, br.s, OH), 2.97(1H, m, $C\text{-}7_A$), 2.81(1H, m, $C\text{-}7_B$), 2.82-2.92(1H, m, C-4 or C-5), 2.55-2.38(2H, m, C-4 or C-5).

Erythro isomer: δ 7.78(1H,dt, J=6.0, 2.5Hz, C-3), 7.27(5H, m, C-H of Ph), 6.20(1H, dt, J=6.0, 2.0Hz, C-2), 4.43(1H, m, C-6), 2.82(2H, m, C-7), 2.64-2.76(2H, m, C-4 or C-5), 2.40(1H, m, C-4, or C-5).

^{13}C-NMR:

Threo isomer: δ 212.8(C-1), 164.9(C-3), 134.0(C-2), 137.8, 129.7, 128.4, 126.5(Carbon of Ph), 73.1(C-6), 48.5(C-5), 41.3(C-7), 32.9(C-4).

Erythro isomer: δ 211.3(C-1), 165.3(C-3), 134.3(C-2), 137.8, 129.7, 128.6, 126.7(Carbon of Ph), 71.2(C-6), 49.7(C-5), 42.0(C-7), 32.0(C-4).

MS(C.I.): $203(M + 1)^+$, $185(M + 1 - H_2O)^+$,

$121(PhCH_2CHOH)^+$, $83(203-121)^+$.

Elemental Analysis:

Found: C 76.9%; H 6.96% ;

Calculated for $C_{13}H_{14}O_2$: C 77.2%, H 6.98%

Preparation of 5-(1-hydroxyundecyl)-cyclopent-2-enone (44) by method A

Starting with cyclopent-2-enone (820mg, 10mmol) and undecanal

(1.87g, 11mmol) by method A, the title compound (44) (2.06g, 72% yield) was obtained as pale yellow oil and characterized as follows:

The ratio of threo/erythro = 81:19

IR: ν_{max}=3460(OH), 1680(C=O), 1580(C=C), cm^{-1}

^{1}H-NMR:

Threo isomer: δ 7.76(1H, dt, J=6.0, 2.5Hz, C-3), 6.20(1H, dt, J=6.0, 2.0Hz, C-2), 3.70(1H, m, C-6), 4.20(1H, br.s, OH), 2.84(1H, ddt, J=19.0, 7.5, 2.0Hz, C-14_A), 2.34-2.46(2H, m, C-4_B,C-5), 1.50(2H, m, C-7), 1.22-1.34(16H, br.s, C-8, C-15), 0.88(3H, t, J=7Hz, C-16).

Erythro isomer: δ 7.78(1H, dt, J=6.0, 2.5Hz, C-3), 6.18(1H, dt, J=6.0, 2.0Hz, C-2), 4.16(1H, dt, J=5.5, 3.5Hz, C-6), 2.68-2.78(2H, m, C-4, C-5), 2.24(1H, m, C-4, or C-5), 1.90(1H, ba.s, OH), 1.48(2H, m, C-7), 1.22-1.34(16H, br.s, C-8 to C-15), 0.88(3H, t, J=7.0Hz, C-16).

^{13}C-NMR:

Threo isomer: δ 213.4(C-1), 164.7(C-3), 133.8(C-2), 72.2(C-6), 49.4(C-5), 35.5(C-7), 32.6(C-4), 31.9(C-8), 29.6(C-9), 29.5(C-10, C-11, C-12), 29.3(C-13), 25.0(C-14), 22.6(C-15), 14.1(C-16).

Erythro isomer: δ 212.1(C-1), 165.7(C-3), 134.4(C-2), 70.2(C-6), 50.6(C-5), 35.1(C-7), 30.1(C-4), 31.9(C-8), 29.6(C-9, C-10, C-11, C-12), 29.4(C-13), 26.1(C-14), 22.7(C-15), 14.1(C-16).

MS(C.I.): 253$(M + 1)^+$, 235$(M + 1 - H_2O)^+$, 171$(C_{11}H_{23}O)^+$, 83$(253 - 171)^+$

Elemental Analysis:

Found: C 75.8%, H, 11.1% ; Calculated for $C_{16}H_{28}O_2$:

C 76.1%; H, 11.2%

Preparation of 2-(t-butyldimethylsilyloxy)-cyclopent 1,3-diene(56a)

To a THF (20ml) solution of LDA (10.5mmol, freshly made from n-BuLi and diisopropylamine at $0^{o}C$), was added a solution of cyclopent-2-enone (0.84ml,10mmol) in THF (5ml) dropwise at $-78^{o}C$. After 10 minutes stirring the solution was quenched with a solution of tert-butyldimethylsilyl chloride (2.83g, 19mmol) and HMPT (1 equivalent) in THF (10ml) at -78°C. The resulting mixture was warmed to RT over one hour with stirring, then diluted with pentane(50ml), washed with water, then brine, dried and concentrated in vacuo to leave the crude product as a yellow oil in 98% yield. This was subjected to a short, flash chromatography (Al_2O_3, pentane), giving the title compound (56a) (1.11g, 58% yield).

The data for (56a) are as follows:

IR: ν_{max} 3080(=C-H), 2960, 2850, 1640(C=C-OR), 1600(C=C), 1540, 1450, 1355cm^{-1}.

^{1}H-NMR (100MHz):

δ 6.28(2H, m, C-1, C-3), 5.33(1H, m, C-4), 2.96(2H, m, C-5), 1.05(9H, s, Me of t-Bu), 0.25(6H, s, Me).

^{13}C-NMR:

δ 156.9(C-2), 133.5(C-1), 132.5(C-3), 104.5(C-4), 37.8(C-5), 25.8, 18.3, 0.1(CH_3-Si).

MS: m/e=196$(M)^{+\cdot}$, 82$(C_5H_6O)^{+\cdot}$

The experiment was repeated under different conditions as described below:

A: Same conditions except the HMPT was replaced by one equivalent of DMPU(dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) with the same result as above.

B: Same condtions except that HMPT(or DMPU) was omitted from the reaction with the result that only a trace of product was detected.

C: Same procedure with B except that DME was used as solvent with the same result as in B.

Preparation of 2-(trimethylsilyloxy)-cyclopenta-1,3-diene(56b)

To a solution of LDA(10.5mmol) in DME(20ml), was added dropwise a solution of cyclopent-2-enone(0.84ml, 10mmol) in DME (5ml) at -78°C. To this solution was added chlorotrimethylsilane (1.85ml, 15mmol) and the resulting mixture was warmed to RT during two hours stirring. After being diluted with pentane (100ml), washed with water, aqueous ammonium chloride, dried over $MgSO_4$ and concentrated in vacuo (which was connected to a nitrogen line) an oily compound (56b) (1.43g, 93% yield) was obtained which is fairly pure from ^{1}H-NMR analysis and ready to be used for further aldol reaction.

The data on (56b) are as follows :

IR: ν_{max} 3150(=C-H), 1640, 1600(C=C), 1370, 1040(O-Si), 842, 864(O-Si)cm^{-1}.

^{1}H-NMR(100MHz):

δ 6.30(2H, m, C-1, C-3), 5.38(1H, m, C-4), 2.99(2H, m, C-5), 0.33(9H, Me of TMS group).

^{13}C-NMR(25MHz):

δ 162.5(C-2), 132.6(C-3), 128.6(C-1), 101.6(C-4), 35.6(C-5).

MS: m/e=154$(M)^{+\cdot}$, 82$(C_5H_6O)^{+\cdot}$.

The experiment was repeated under different conditions as described below:

A: Using THF as solvent and the same procedure.Result: 76% yield of (56b).

B: Using THF as solvent and work-up without being diluted with pentane. Result: instead of(56b), cyclopent-2-enone was the major component in the crude product (detected by ^{1}H-NMR).

C: Using THF + DMPU (1 equivalent) as solvent. Result: same as above but compound contained a certain amount of DMPU.

D: Using NaH as base out at 0°C instead of -78°C. Result: a multi-component mixture resulted.

Attempted aldol reaction of (56a) and benzaldehyde mediated by $TiCl_4$

A DCM (10ml) solution of (56a) (0.49g, 2.5mmol) was added

dropwise into a mixture of benzaldehyde (0.292g) and $TiCl_4$ (0.55g, 2.75mmol) in DCM(20ml), under an atmosphere of argon at $-78^{o}C$ and the reaction mixture was stirred for 1hr.. After hydrolysis at that temperature by adding AcOH(1ml) in water(10ml), the resulting organic layer was extracted with ether, and the extract was washed with water and dried over anhydrous $MgSO_4$. The mixture was evaporated under reduced pressure. No desired aldol product could be isolated by chromatography, and only a trace of starting (56a) and benzaldehyde were detected by ^{1}H-NMR(60MHz) of the crude product.

This reaction was repeated under different conditions as described below:

A. Same conditions, but reactants were added in the reverse order. Same result as above.

B. Same condition except that THF was used as solvent instead of DCM. Similar result as above.

C. Same procedure, but using TBAF(1 equiv.) instead of $TiCl_4$. Result: similar to B.

D. Same procedure, but using TMS-triflate as catalyst instead of $TiCl_4$. Similar results to those as described above.

<u>The Aldol Reaction of 1-trimethlsilyloxycyclopenta-1,3-diene (56b) with aldehydes mediated by $TiCl_4$ [A general procedure for preparing compounds (57) to(60)]</u>

To a DCM(20ml) solution of (56b) (0.77g, 5mmol) and

benzaldehyde 0.58g, 5.5mmol) was added dropwise a DCM(5ml) solution of $TiCl_4$(1.1g, 5.5mmol) at -78°C, and the reaction was stirred for 1hr. at that temperature. After the usual work-up, the resulting mixture was chromatographed on silica gel. Elution with Pet. ether/EtOAC; 9:1 to 1:3, afforded 413mg(44%) of (57) as a pale yellow oil (a pair of diasteroisomers, threo / erythro = 82:18) which has identical spectral data with compound (42).

This reaction of (56b) and benzaldehyde was repeated under the same procedure but mediated by various Lewis bases. The yields and diastereoisomeric ratios of the corresponding aldols are listed in Table IX.

The reactions of silyl enol ether (56b) with various aldehydes were carried out affording the yields and the diastereoisomeric ratio of the corresponding aldols are listed in Table VIII and Table X. The spectropic data on (58), (59) and (60) were identical to the compounds (43), (41) and (40).

Attempted preparation of the deconjugated aldol (66) via mono-anion enolate

A General procedure:

A solution of 2-cyclopentenone (15) (410mg, 5mmol) in THF(5ml) was added dropwise into a solution of LDA(5.5mmol)in THF (15ml) at-78°C, under an atmosphere of argon.The

resulting mixture was stirred (RT, 0.5hr. and 0°C, 1hr.), then a THF(10ml) solution of benzaldehyde (530mg, 5mmol) was added dropwise at -78°C. After 10 minutes stirring, the resulting mixture was quenched with aqueous NH_4Cl at -78°C and the organic layer was extracted with ether, washed with brine and dried over anhydrous $MgSO_4$. The mixture was evaporated under reduced pressure and no desired deconjugated product (66) could be detected by ^{1}H-NMR(60MHz) on the crude product. Instead, its spectroscopic data was identical to the 5-substituted aldol product (42). The experiment was repeated under various conditions (Table XI), and the corresponding results are listed in Table XI.

Attempted preparation of cyclopent-3-enone (23') via the deconjugation of cyclopent-enone(15)

General procedure:

A solution of 2-cyclopentenone (15) (82mg, 1mmol) in THF (1ml) was added dropwise into a solution of NaOMe(1.2mmol) in MeOH (5ml) at -78°C under an atmosphere of nitrogen. The resulting mixture was stirred (-78°C, 1h and 0°C, 2h) and quenched at -78°C with a THF (1.2ml) solution of AcOH (1.2mmol). The mixture was concentrated in vacuo under 30°C. The residue was extracted with ether washed with brine, dried over anhydrous $MgSO_4$, and the solvent was once again removed in vacuo giving a multi-component mixture. The crude product showed no spectroscopic evidence for the

formation of the desired product. Its ^{1}H-NMR(60MHz) did not show chemical shifts for the two unconjugated vinylic protons of (23′) between 6.0-5.6ppm. Only small amount of (15) was found along with much resinous material.

This reaction was repeated under different conditions as described below:

A. Same procedure except that NH_4Cl-H_2O was used as quenching reagent instead of HOAc-THF.

Result: same as above.

B. Same procedure but using t-Butyl iodide as a quenching reagent.

Result: same as above.

C. Using the following reagents, NaH(1 equiv), DME(10ml), (-78^{o}C,2h); AcOH(1 equiv.), THF(-78^{o}C).

Result: same as above.

D. Using the following reagents, NaH(1 equiv.), DME(10ml), (-70^{o}C, 0.5h; 0^{o}C, 1h); AcOH(1 equiv.), THF(-78^{o}C).

Result: same as above.

E. Using the following reagents, NaH(1 equiv.), DMF(10ml) (0^{o}C, 2h); AcOH(1 equiv.), THF(-20^{o}).

Result: same as above.

F. Using the following reagents, NaH(1 equiv.) DMF(10ml) (0^{o}C, 1h); then addition of THF(20ml); AcOH(1 equiv.), THF(-78^{o}C).

Result: same as above.

G. Using the following reagents and the same conditions as F, but quenched with Me_3C-I at -78^{o}C instead of AcOH-THF.

Result: same as above.

H. Using the following reagents, NaOH(1 equiv.)/TBAF/H_2O /THF(0^oC,2h; RT,5h), NH_4Cl-H_2O(0^oC).

Result: same as above.

I. Using the following reagents, t-BuOK(1 equiv.)-t-BuOH(5ml) (0^oC, RT, 2h), then THF(20ml) was added before quenching with AcOH-THF(-70^oC).

Result: same as above.

J. As I, except being quenched with t-butyl iodide at -70^oC instead of AcOH-THF.

Result: same as above.

Attempted preparation of (69) via dianion reaction.

Method A:

To a solution of LDA(5.5mmol) in THF(10ml) was added dropwise a THF(5ml) solution of cyclopent-2-enone(410mg, 5mmol) at -78^oC under an atmosphere of argon. The resulting mixture was stirred (0.5h, -78^oC) , then a solution of benzaldehyde (530mg, 5mmol) in THF(5ml) was introduced dropwise while stirring (20min.). One more equiv. of LDA in THF(5ml) was added dropwise at -78^oC and the resulting mixture was continuously stirred (1h, -78^oC) before it was quenched with AcOH(11mmol) in THF(1.1ml) at that temperature.

A brown oil as crude product (611mg, 65%) was obtained after usual work-up and was identical to the compound (42). No desired deconjugated aldol (69) could be detected from its ^{1}H-NMR(60MHz) spectrum.

Method B:

To a solution of LDA(5.5mmol) in THF(10ml) was added dropwise a THF(3ml) solution of cyclopent-2-enone (205mg, 2.5mmol) at -78^0C under an argon atmosphere. The resulting mixture was stirred (-78^0C,3h) and a solution of benzaldehyde(265mg, 2.5mmol) in THF(3ml) was introduced dropwise while stirring (10min). After an additional 5min. stirring, the resulting mixture was quenched (-78^0C) with NH_4Cl-H_2O and worked-up as usual, a multi-component mixture resulted. No desired deconjugated aldol (69) could be detected from the ^{1}H-NMR (60MHz) spectrum of the crude product.

This reaction was repeated under different conditions as described below:

A. Same conditions, but quenched with AcOH(2 equiv.)-THF.
   Result: same as above.

B. Same conditions, but quenched with Me_3CI
   Result: same as above.

C. 2 equivs LDA, 1 equiv. cyclopentenone (-78^oC, 1h; -20^oC, 1h), 1 PhCHO (dropwise, -78^oC, then stirred 10min.more), quenched with AcOH(2 equiv.)-THF(-78^oC).
   Result: same as above.

Preparation of 5-ethoxycarbonyl-cyclopent-2-enone (78)

Method A:

To a THF (30ml) solution of LDA(11mmol) was added dropwise a solution of cyclopent-2-enone(0.86ml, 10mmol), in THF(20ml) at -78°C under an atmosphere of nitrogen with stirring. The resulting mixture was stirred(-78°C, 0.5 h) and a solution of ethyl chloroformate (1.2g, 11mmol) in THF (4ml) was added. After stirring (-78°C, 1 h), the resulting mixture was quenched with aqueous citric acid (20ml of 10% solution) and worked-up as normal. A pale yellow oil (0.64g, 42%) was isolated from column chromatography (silica gel, pet. ether / ether = 17:3) and identified as compound (79)[2-ethoxycarbonyl-cyclopenta-1,3-diene] from the following data. No desired (78) could be isolated from reaction.

IR: ν_{max} 3080(=C-H), 1755(C=O), 1600(C=C), 1365, 1270, 1230 cm^{-1}.

^{1}H-NMR (100 MHz):

δ 6.48(1H, d, J=3Hz, C-3), 6.42(1H, m, C-1), 6.04(1H, m, C-4), 4.27(2H, q, J=7Hz, O-CH_2-), 3.05(2H, dd, J=3 and 3.5Hz, C-5), 1.34(3H, t, J=7Hz, CH_3).

^{13}C-NMR (22.5 MHz):

δ 152.7(CO_2Et), 152.2(C-2), 133.8(C-3), 129.1(C-1), 112.5(C-4), 64.6(OCH_2-), 38.1(C-5), 14.2(-CH_3).

MS: m/e = 154$(M)^{+\cdot}$, 108$(M - C_2H_6O)^{+\cdot}$, 82$(C_5H_6)^{+\cdot}$.

Elemental Analysis:

Found: C 62.5%; H 6.61%.

Calculated for $C_8H_{10}O_3$: C 62.3%; H 6.49%.

Method B:

Using the same experimental procedure described in Method A and employing diethyl pyrocarbonate (80) as a reagent instead of ethyl chloroformate, compound (79) (0.81mg, 5.3mmol, 53%) together with a new compound (0.11g, 0.7mmol, 7%) was isolated as a yellow oil(Rf=0.15, silica gel, 15% ether in pet. ether) and identified as the desired (78) from following data:

The ratio of (78) / (79) = 12 : 88.

IR: ν_{max} 3400(=C-OH), 3080(=C-H), 1755(C=O of Carboxyl group), 1700(C=O of ketone), 1610(C=C), 1365cm^{-1}.

^{1}H-NMR (60 MHz):

δ 7.80(1H,m, C-3), 6.18(1H,m, C-2), 4.22(2H,q, J=7Hz, O-CH_2-), 3.40(1H, dd, J=6.5 and 5Hz, C-5), 3.30(2H, m, C-4), 1.28(3H, t, J=7Hz, CH_3).

^{13}C-NMR (22.5 MHz):

δ 164.3(C-3), 132.6(C-2), 61.6(O-CH_2), 50.9(C-5), 33.2(C-4), 14.1(CH_3).

MS: m/e=154$(M)^{+\cdot}$, 108$(M - C_2H_6O)^{+\cdot}$, 82$(C_5H_6O)^{+\cdot}$.

Elemental analysis: Found: C 62.5%; H 6.21%.

Calculated for $C_8H_{10}O_3$: C 62.3%; H 6.49%.

This reaction was repeated under different conditions as described below:

(A). Same experimental procedure as Method B and using lithium dicyclohexylamide as base instead of LDA. Result: (78)(0.2g, 13%) / (79)(0.14g, 9.1%) = 20 : 80

(B). Same experimental procedure as Method B, using ether as solvent and lithium dicyclohexylamide as base. Result: (78)(0.16g, 10%) / (79)(0.14g, 9%) = 53 : 47.

(C). Same condition as (A) for generating the lithium carbanion of cyclopent-2-enone, the resulting mixture was stirred (-78^{o}C, 0.5 h; -20^{o}C, 10 min) and a solution of diethylpyrocarbonate was introduced (-20^{o}C). Result: (78) (0.42g, 27%) but no (79) could be isolated from the reaction.

Attempted preparation of 5,5-diethoxycarbonyl-cyclopent-2-enone (74)

To an ether(30ml) solution of LDA (22 mmol), was added dropwise a solution of cyclopent-2-enone (0.86ml, 10mmol) and diethylpyrocarbonate 83.2g, 20mmol) in ether. After stirring (-20^{o}C,1h), the resulting mixture was quenched with aqueous citric acid (10%) and worked-up as normal. Along with (78)(0.31g, 20%), a pale yellow oil (0.39g, 17%) was isolated and identified as the compound (81) [1-ethoxycarbonyl-

2-carbethoxycyclopent-1,3-diene] from the following data, No desired (74) could be isolated.

IR: ν_{max} 3080(=C-H), 1760-1690(br.s, C=O), 1620, 1590(C=C) cm^{-1}.

^{1}H-NMR (60 MHz):

δ 7.86(1H, m, C-4), 6.24(1H, m, C-3), 4.21(2H, q, J=7Hz,O-CH_2-), 4.18(2H,q, J=7Hz, O-CH_2-), 3.20(2H,m, C-5), 1.28(3H, t, J=7Hz, CH_3), 1.25(3H, t, J=7Hz, CH_3).

MS : m/e=226($M^{+\cdot}$), 180(1), 154(30), 109(57), 108(68), 83 (68), 82(100), 29(98), 27(76).

This reaction was repeated using (78) as starting compound, treated with LDA(1 equiv., -78°C), quenched with (80) (-20°C), then stirred(-20°C,1h) before the usual work-up. Result: same as above.

Preparation of 2-(hydroxybenzyl)-cyclopent-3-enone (88) via the enolsilane carbanion

To a solution of LDA(5.5mmol) in THF(15ml), was added dropwise to a solution of (56b)(0.8g, 5mmol) in THF(8ml) at -78°C under an atmosphere of nitrogen. The resulting mixture was stirred (-78°C,2h), a THF(5ml) solution of benzaldehyde (0.53ml, 5mmol) was introduced dropwise while stirring (-78°C). After an additional 10 minutes of stirring, the resulting mixture was quenched with AcOH (5.5mmol) in THF

(5.5ml) and worked up as usual. The crude product (0.79g, 84%) was obtained as brown oil and identified as a pair of regio-isomers: the conjugated aldol(89) and the deconjugated (88) ((88) / (89) = 3 : 1 , determined from ^{1}H-NMR spectra). The compound (89) was confirmed since it had identical spectra data with compound (42). The deconjugated (88) was confirmed from the following ^{1}H-NMR (60 MHz) of the crude product:

δ 7.20(5H, s, CH of Ph), 5.95(2H, m, two =C-H of C-3 and C-4), 4.50(1H, m, C-6), 3.60(1H, br.s, OH), 2.10-2.70(3H, m, 3H, C-2 and C-5).

The crude product (0.5g) was subjected to flash column chromatography (silica gel, pet. ether / ether = 4:1 - 1:3) and the desired compound (88) disappeared during the separation, in its placed, along with the conjugated compound (89)(60mg,12%), a new compound (90)(115mg , 23%) was isolated which had the identical spectral data with that anticipated for compound (54).

Alumina (neutral, basic) packing were also employed for the same purpose, again, similar results were obtained in every case.

Due to our inability to separate the deconjugated aldols, no further efforts were given to this field.

Preparation of 5-(1´-hydroxyhexyl)-cyclopent-2-enone (95)

The experimental procedure for this reaction was the same as that for the preparation of 5-(1´-hydroxyethyl)cyclopent-2-enone(39) on a 10 mmol scale, and the desired aldol (95) (1.15g, 73%, threo / erythro = 83:17) was isolated as a pale yellow oil and its structure confirmed from following data:

IR: ν_{max} 3450(br., OH), 1675(C=O), 1580(C=C), 1450, 1420, 1340 cm^{-1}

^{1}H-NMR:

Threo isomer: δ 7.75(1H, dt, J=4.5 and 2.0Hz, C-3), 6.21(1H, dt, J=4.5 and 2Hz, C-2), 4.22(1H, s, OH), 3.70(1H, dt, J=7 and 3.5Hz, C-6), 2.83(1H, ddd, J=15.5, 2.0 and 1.5Hz, C-4_A), 2.41(1H, dm, J=15.5Hz, C-4_B), 2.37(1H, m, C-5), 1.50(2H, m, C-7), 1.32(6H, s, C-8 to C-10), 0.90(3H, t, J=6.5Hz, C-11).

Erythro isomer: δ 7.80(1H, dt, J=4.5 and 2Hz, C-3), 6.21(1H, m, C-2), 4.16(1H, br.s, OH), 3.70(1H, m, C-6), 2.71(1H, m, C-5), 2.40(2H, m, C-4), 1.50(2H, m, C-7), 1.32(6H, br.s, C-8 to C-10), 0.90(3H, d, J=6.5Hz, C-11).

^{13}C-NMR:

Threo isomer: δ 213.4(C-1), 164.8(C-3), 133.7(C-2), 72.1(C-6), 49.4(C-5), 35.3(C-7), 32.5(C-9), 31.7(C-4), 24.6(C-8), 22.5 (C-10), 14.0(C-11).

Erythro isomer: δ 211.6(C-1), 165.4(C-3), 134.0(C-2), 71.0(C-6), 50.0(C-5), 34.9(C-7), 32.5(C-9), 31.6(C-4), 24.6

(C-8), 22.5(C-10), 13.9(C-11).

MS(C.I.): 183$(M+1)^+$, 165$(M+1-H_2O)^+$, 101(side chain)$^+$, 83(M+1-side chain)$^+$.

Preparation of 2-(1´-hydroxyhexyl)-4-phenylthio-cyclopentanone (96)

To a solution of aldol (95)(0.91g, 5mmol) in $CHCl_3$ (20ml) was added dropwise a solution of thiophenol (0.52ml), while stirring. The reaction was warmed to RT with stirring (2 h) and followed by TLC. The resulting mixture was then diluted with DCM (20ml), washed with 5% sodium hydroxide solution (2 X 20 ml) and dried over magnesium sulphate. After the usual work-up and chromatography, a brown oil (0.782g,54%) was isolated giving one spot on TLC (Rf=0.47, silica gel, pet. ether) and identified as the title compound (96) from following data:

IR: ν_{max} 3450(br., OH), 3050, 1720(C=O), 1575(C=C) cm^{-1}

^{1}H-NMR (60 MHz):

δ 7.4(5H, m, CH of Ph), 4.2(1H, br.s, OH), 3.8(2H, m, C-6), 2.5(6H, m, C-2 and C-4 and C-7), 1.4(6H, m, C-8 to C-10) 0.90(3H, t, J=7Hz, C-11).

MS : m/e=292$(M)^{+\cdot}$, 274$(M - H_2O)^{+\cdot}$, 164$(274 - PhSH)^{+\cdot}$, 121 $(164-C_3H_7)^+$, 109$(PhS)^+$, 82$(C_5H_6O)^{+\cdot}$, 77$(Ph)^+$

Prpearation of 6-(1'-Hydroxyhexyl)-3,4,5,6-tetrahydro pyranone (97) via oxidation reaction

To a DCM (6ml) solution of (96)(285mg, 1mmol) which contained sodium bicarbonate (0.3g, 1mmol) as a buffer, a solution of mCPBA (0.6g, >3 equiv.) in DCM (5ml) was added at $0^{o}C$ under a nitrogen atmosphere. The resulting mixture was stirred (RT, 20 h) and followed by TLC (silica gel, pet. ether). The reaction was worked up by being extracted with DCM (50ml), washed with 0.1M HCl (3 X 15ml) and brine, dried over $MgSO_4$ and concentrated in vacuo. The title compound (97)(58.5mg, 17%) was isolated as a yellow oil and appeared as one major spot on TLC (Rf=0.16, silica gel, pet. ether).

IR: ν_{max} 3560(OH), 1735(C=O), 1580(C=C), 1305 and 1150 ($-SO_2Ph$), 1060(-S=O-) cm^{-1}.

^{1}H-NMR:

Major isomer: δ 7.79(2H, m, o-Ar-H), 7.73(1H, m, p-Ar-H), 7.62(2H, m, m-Ar-H), 4.20(1H, dt, J=9.5 and 2.5Hz, C-6), 3.58(1H, m, C-7), 3.00(1H, br.s, OH), 2.75(2H, m, C-3), 2.25(2H, m, C-5), 1.54(2H, m, C-8), 1.30(6H, m, C-9 to C-11), 0.89(3H, d, J=7Hz, C-12).

Minor isomer: δ 7.79(2H,m,o-Ar-H), 7.73(1H,m, p-Ar-H), 7.62(2H, m, m-Ar-H), 4.45(1H, dt, J=7.5 and 2.5Hz, C-6), 3.75 (1H, m, C-7), 3.00(1H, br.s, OH), 2.86(1H, dd, J=12.5 and 5.5Hz, $C-3_A$), 2.65(1H, dd, J=12.5 and 8.0Hz, $C-3_B$), 2.25 (2H, m, C-5), 1.54(2H, m, C-8), 1.30(6H, m, C-9 to C-11), 0.89

(3H, d, J=7Hz, C-12).

^{13}C-NMR:

Major isomer: δ 167.6(C-2), 135.2(C(1) of Ph), 129.7, 129.0 and 128.7(carbons of Ph), 80.9(C-6), 72.7(C-7), 56.4 (C-4), 32.6(C-3), 31.6(C-10), 29.7(C-5), 28.1(C-8), 24.1(C-9), 22.5(C-11), 13.9(C-12).

Minor isomer: δ 168.9(C-2), 136.4, 129.7, 129.0 and 128.7(Carbons of Ph), 78.9(C-6), 72.7(C-7), 54.4(C-4), 33.3(C-3), 31.6(C-10), 29.3(C-5), 25.1(C-8), 24.1(C-9), 22.5 (C-11), 13.9(C-12).

MS(C.I.):341$(M+1)^+$, 199$(M+1-PhSO_2H)^+$, 181$(199-H_2O)^+$,
156 $(199-C_3H_7)^+$, 129 $(199-C_5H_{10})^+$,
98 $(C_5H_6O_2)^+$

Preparation of 6-(1'-hydroxyhexyl)-5,6-dihydropyran-2-one (98)

To a solution of sulphone (97)(40mg, 0.12mmol) in chloroform (6ml), was added 0.035ml (2 equiv.) of diazabicycloundecene at 0°C with stirring. The resulting mixture was stirred (0°C to RT, 20 h; 40°C, 1 h), then one more equiv. of diazabicycloundecene (0.013 ml) was added and stirred (40°C, 1 h). The reaction mixture was then diluted with chloroform (10ml), washed with 1M HCl (2 X 10ml), saturated $NaHCO_3$ solution (2 X 10ml), dried over $MgSO_4$ and concentrated in vacuo. After purification of the crude product by flash chromatography (silica gel, pet. ether), a yellow oil (13mg, 56%) as one spot by TLC (Rf=0.33) was isolated and identified as the desired (98) from following data:

IR: ν_{max} 3570(OH), 1705(C=O), 1365, 1240, 1070, 1050, 1020 cm^{-1}.

^{1}H-NMR:

δ 6.96(1H, ddd, J=7.5, 5.5 and 2.0Hz, C-4), 6.04(1H, ddd, J=7.5, 2.0 and 1.0Hz, C-3), 4.35(1H, ddd, J=10.0, 3.0 and 3.0Hz, C-6), 3.65(1H, m, C-7), 2.62(1H, dddd, J=15.0, 10.0, 2.0 and 2.0Hz, C-5_A), 2.30(1H, dddd, J=15.0, 5.5, 3.0 and 1.0Hz, C-5_B), 2.20(1H, s, OH), 1.58(4H, m, C-8 and C-9), 1.33(4H, m, C-10 and C-11), 0.90(3H, t, J=6.5Hz, C-12).

^{13}C-NMR:

δ 163.9(C-2), 145.5(C-4), 121.0(C-3), 80.5(C-6), 72.6(C-7), 32.6 (C-8), 31.7(C-5), 26.0(C-9), 25.1(C-10), 22.6(C-11), 14.0(C-12).

MS: m/e=198$(M)^{+\cdot}$, 180$(M - H_2O)^{+\cdot}$.

Preparation of butenolide (99)

Following the standard method[60] and starting from furfural (96g, 1mol), the desired (99)(b.p. 95-96°C/19mmHg, 45g, 54%) as a slightly yellow oil was obtained. The spectral data was in agreement with published data[60].

Preparation of 2-trimethylsilyloxy-furan (101)

To a pre-cooled (0°C) mixture of triethylamine (28.7ml, 205mmol) and chlorotrimethylsilane (26.2ml, 202mmol), was added dropwise the butenolide (99)(16.8g, 200mmol) under

nitrogen with stirring. The reaction was stirred (RT, 5h) and then extracted quickly and thoroughly with pentane (3 X 100ml) and ether (3 X 50ml). The white solid of triethylamine hydrochloride was filtered in vacuo and the solvent evaporated at RT. The crude product(38.58g) was obtained as a yellow oil which contained a small amount of triethylamine and was found to be pure enough for further reaction without purification. The product was dissolved in DCM and stored at $0^{o}C$ under nitrogen.

^{1}H-NMR(100 MHz):

δ 6.70(1H, d, J=2.5Hz, C-3), 6.08(1H, dd, J=2.5 and 4.0Hz, C-4), 5.00(1H, d, J=4.0Hz, C-5), 0.21(9H, s, Me of TMS group).

The spectral data was in agreement with the literature data[59].

This reaction was repeated under different conditions described as follows:

(A). By generating the carbanion of furanone with LDA at $-78^{o}C$, then quenching with TMSCl Result: a mixture of (99) and (101) was generated.

(B). Furanone (99) was treated with NaH/DMF at $0^{o}C$, then quenched with TMSCl. Result: very poor conversion into (101) was obtained.

Preparation of 5-(1´-hydroxybenzyl)-butenolide (104)

via $ZnCl_2$ mediated condition

To a THF (50ml) solution of benzaldehyde (1.06g, 10mmol) which contained 1.71g of zinc chloride (13mmol), was added 2-trimethylsilyloxyfuran(1.57g, 10mmol) at RT with stirring under an atmosphere of nitrogen. The resulting mixture was heated under reflux (3 h) and quenched with aqueous $NaHCO_3$ solution. After the usual work-up, a pale yellow oil (0.6g, 32%) was isolated after chromatography and identified as compound (104)(a pair of diastereoisomers, threo/erythro = 3:2) from following data:

IR: ν_{max} 3430(OH), 3070(=C-H), 1745(C=O) cm^{-1}.

^{1}H-NMR:

Threo isomer: δ 7.31-7.38(5H, m, CH of Ph), 7.16(1H, dd, J=5.5 and 2.0Hz, C-4), 6.07(1H, dd, J=5.5 and 2.0Hz, C-3), 5.15(1H, ddd, J=7.0, 2.0 and 2.0Hz, C-5), 4.69(1H, d, J=7.0Hz, C-6), 3.40(1H, br.s, OH).

Erythro isomer: δ 7.31-7.38(5H,m, CH of PH), 7.16(1H, dd, J=6.0 and 2.0Hz, C-4), 6.13(1H, dd, J=6.0 and 2.0Hz, C-3), 5.16(1H, ddd, J=5.0, 2.0 and 2.0Hz, C-5), 5.06(1H, d, J=5.0Hz, C-6), 3.26(1H, br.s, OH).

^{13}C-NMR:

Threo isomer: δ 173.2(C-2), 153.3(C-4), 137.8, 128.8, 126.7 and 126.0(carbons of Ph), 122.8(C-3), 86.6(C-5), 75.3 (C-6).

Erythro isomer: 173.7(C-2), 152.9(C-4), 137.9, 128.7 128.4 and 126.3(carbons of Ph), 123.1(C-3), 86.9(C-5), 72.9 (C-6).

MS(C.I.): 191$(M+1)^+$, 173$(M + 1 - H_2O)^+$, 107(side chain)$^+$, 85$(C_4H_4O_2 + 1)^+$.

Preparation of 5-(acetoxyphenylmethyl)-butenolide (106)

To a solution of acetyl chloride(0.16g,2mmol) and (104)(0.38g, 2mmol) in THF(10ml), was added 0.2ml of pyridine at 0^0C with stirring. The resulting mixture was stirred (0^0C to RT, 5 h) and then diluted with DCM(40ml), washed with 10% HCl, aqueous $NaHCO_3$ solution and brine. After the usual work-up and flash chromatography, a pale yellow oil was isolated (0.25g, 54%) and identified as the desired (106) from the following data:

IR: ν_{max} 3030-3080(=C-H), 1755(C=O), 1700, 1600(C=C) cm^{-1}

^{1}H-NMR:

Threo isomer: δ 7.36(5H, m, CH of Ph), 7.22(1H, dd, J=6.0 and 1.5Hz, C-4), 6.14(1H, dd, J=6.0 and 2.0Hz, C-3), 5.88(1H, d, J=6Hz, C-6), 5.30(1H, ddd, J=6.0, 2.0 and 1.5Hz, C-5), 2.11(3H, s, CH_3CO-) ppm.

Erythro isomer: δ 7.36(5H, m, CH of Ph), 7.22(1H, dd, J=6.0 and 1.5Hz, C-4), 6.12(1H, dd, J=6.0 and 2.0Hz, C-3), 6.08(1H, d, J=4Hz, C-6), 4.86(1H, ddd, J=4.0, 2.0 and 1.5Hz, C-5), 2.12(1H, s, CH_3CO-) ppm.

^{13}C-NMR:

Threo isomer: δ 172.1(C-2), 169.5(C=O of Ac group),

152.4(C-4), 148.2(C-1 of Ph), 129.2, 128.8 and 127.1(carbons of Ph), 123.4(C-3), 84.0(C-5), 74.6(C-6), 20.9(Me group) ppm

Erythro isomer: δ 170.5(C-2), 169.5(C=O of Ac group), 151.6(C-4), 147.5(C-1 of Ph), 129.2, 128.8 and 127.1(carbons of Ph), 122.0(C-3), 84,5(C-5), 74.0(C-6), 20.9(Me group)ppm.

The ^{1}H-NMR data of (106) was identical with the literature data[58]. The literature method[58] was followed in 6 mmol scale and the desired (105) was obtained as a yellow oil(0.2g, 14%) and had identical spectral data to (106).

Preparation of 5-(1´-hydroxyethyl)-butanolide (108) via hydrogenation of (107)

Following the experimental procedure described for the preparation of (24) and starting with a mixture of 5-(1´-hydroxyethyl)-butenolide (107)(threo/erythro = 10:1, 0.41g, 3.2mmol) and 10% Pd on C(45mg) in EtOAc, the hydrogenation went smoothly(RT, 1 at.) and reached completion in 3 hours. After the usual work-up as described for the preparaton of (24), a pale yellow oil (0.41g, >98%, threo/erythro = 10:1) was obtained and identified as the title compound (108) from the following data:

IR: ν_{max} 3400(OH), 1760(C=O) (or 1770 in $CHCl_3$) cm^{-1}

^{1}H-NMR:

Threo isomer: δ 4.32(1H, m, C-5), 3.74 (1H, dq, J=7.0 and 6.5Hz, C-6), 3.31(1H, br.s, OH), 2.50(2H,m, C-3), 2.19(1H, m, C-4_A), 1.99(1H, m, C-4_B), 1.18(3H, d, J=6.5Hz, C-7)

Erythro isomer: δ 4.33(1H, m, C-5), 4.03(1H, dq, J=6.5 and 3.5Hz, C-6), 3.31(1H, br.s, OH), 2.55(2H, m, C-3), 2.30(1H, m, C-4_A), 2.12(1H, m, C-4_B), 1.11(3H, d, J=6.5Hz, C-7).

^{13}C-NMR:

Threo isomer: δ 177.6(C-2), 84.2(C-5), 69.4(C-6), 28.5 (C-3), 23.8(C-4), 118.3(C-7).

Erythro isomer: δ 177.9(C-2), 83.6(C-5), 67.1(C-6), 28.5(C-3), 20.9(C-4), 17.7(C-7).

MS: m/e= 130$(M)^{+\cdot}$, 112$(M - H_2O)^{+\cdot}$, 86(M-side chain)$^{+\cdot}$

Preparation of 5-(1´-hydroxyundecyl)-butenolide (116)

To a DCM (10ml) solution of 2-trimethylsilyloxyfuran (101) (2.355g, 15mmol) and undecanal(18mmol), stannic chloride(5 drops) was added under an atmosphere of argon at -78°C with stirring. The reaction mixture was stirred (1 h), quenched with saturated sodium metabisulphite solution (20ml) at -78°C, and then extracted with ether(3 X 20ml). After the usual work-up, a white solid (m.p.91-91.5°C,3.056g,80%) (116), was obtained along with 0.873g of (99) . The overall yield is 86% after being corrected for the recovery of (99) . The ratio of threo /erythro is over 98:2 by temperature

programmed GLC analysis[Programme:140°C(4min)--(10°C/min) --240°C(10min)--(20° C/min)--280°C(5min)].

IR : ν_{max} 3360 (OH), 3100, 1715(C=O), 1600, 1375 cm^{-1}

^{1}H-NMR :

Threo isomer: δ 7.50(1H, dd, J=7.0 and 1.7Hz, C-4), 6.17(1H, dd, J=7.0 and 2.0Hz, C-3), 5.12(1H, ddd, J=5.0, 2.0 and 1,5Hz, C-5), 3.83(1H,br.m, C-6), 2.97(1H, br.s, OH), 1.58(2H, m, C-7), 1.28(16H, br.s, C-8 to C-15), 0.89(3H, t, J=6.5Hz, C-16).

^{13}C-NMR:

Threo isomer: δ 173.4(C=O), 154.3(C-4) , 122.5 (C-3), 86.4(C-5), 71.6(C-6), 33.2(C-7), 31.9, 29.6, 29.5, 29.3, 25.6, 22.7, 14.1(CH_3).

MS(C.I.): 255$(M + 1)^+$, 237$(M + 1 - H_2O)$, 171(side chain)$^+$, 84$(C_4H_4O_2)^+$.

Elemental analysis: Found : C 70.9%; H 10.2%.

Calculated for $C_{15}H_{26}O_3$: C 70.9%; H 10.2%.

Preparation of 5-(1´-hydroxyundecyl)-butanolide (124) via hydrogenation of (116)

Following the experimental procedure described for the preparation of (24) and starting with (116)(0.45g, 1.78mmol) and 10% Pd on C (50mg) in EtOAc, the hydrogenation went smoothly (RT, 1 at.) and reached completion in 3 hours. After work-up, the desired (124)(0.45g, >98%) was isolated as a white powder and confirmed as the threo isomer by a comparison

of its ^{1}H-NMR data with literature data[62].

IR : ν_{max} 1735(C=O) cm^{-1}

^{1}H-NMR:

Threo isomer: δ 4.43(1H, dt, J=7.0 and 4.5Hz, C-5), 3.57(1H, dt, J=6.5 and 4.5Hz, C-6), 2.57(2H, m, C-3), 2.54(1H, br.s, OH), 2.20(2H, m, C-4), 1.53(2H, m, C-7), 1.28(16H, br.s, C-8 to C-15), 0.88(3H, t, J=7Hz, C-16).

^{13}C-NMR:

Threo isomer: δ 177.6(C-2), 83.1(C-5), 73.5(C-6), 33.0(C-4), 31.9(C-3), 29.6, 29.5, 29.3, 28.7, 25.5, 24.1 and 22.7(C-7 to C-15), 14.1(C-16).

Preparation of 5-(1'-hydroxyethyl)-butenolide (136)

To a solution of 2-trimethylsilyloxyfuran(0.314g,2mmol) in DCM (5ml, freshly distilled from P_2O_5) and ethanol(0.097g, 2.4mmol), was added stannic chloride (2 drops) under an atmosphere of argon at -78°C with stirring. The reaction mixture was stirred (1 h, -78°C), then quenched with water (5ml) before it was warmed to room temperature. The aqueous phase was separated and the organic phase was extracted with water (4 X 10ml). The organic phase was dried over magnesium sulphate and the solvent was evaporated, a yellow oil (0.056g) was obtained and identified as the compound (99) . The aqueous phase was combined and evaporated to dryness in vacuo. The semi-solid residue was extracted with ethyl acetate (40ml) and dried over magnesium sulphate . After evaporation and short

column chromatography (silica gel, DCM / EtOAc = 20:1 to 4:1), the title compound(136) (0.17g,67%) was obtained as a pale yellow oil. After correction for the recovery of compound(99), the overall yield is over 95%. The ratio of threo / erythro is 87:13 as determined by temperature programmed GLC analysis[programme:80°C(5min)--(5°C/min)--130°C--(20°C/min)--200°C].

IR: ν_{max} 3410(OH), 3100, 2850-2965, 1785, 1740. cm^{-1}

^{1}H-NMR:

Threo isomer: δ 7.46(1H, dd, J=1.5 and 6.0Hz, C-4), 6.20(1H, dd, J=2.0 and 6.0Hz, C-3), 4.94(1H, ddd, J=1.5, 2.0 and 5.5Hz, C-5), 3.94(1H,dq, J=5.5 and 6.5Hz, C-6), 2.43(1H, s, OH), 1.33(3H, d, J=6.5Hz, C-7).

Erythro isomer: δ 7.59(1H, dd, J= 1.0 and 6.0Hz, C-4), 6.20(1H, dd, J=2.0 and 6.0Hz, C-3), 4,96(1H, ddd, J=1.0, 2.0 and 5.0Hz, C-5), 4.06(1H, dq, J=5.0 and 6.5Hz, C-6), 2.97(1H, s, OH), 1.32(3H, d, J=6.5Hz, C-7).

^{13}C-NMR :

Threo isomer: δ 173.5(C=O, C-2), 153.4(C-4), 122.9(C-3), 87.1(C-5), 68.3(C-6), 18.8(C-7).

Erythro isomer: δ 173.2(C=O,C-2), 153.6(C-4), 122.7(C-3), 86.9(C-5), 67.5(C-6),18.8(C-7).

MS(C.I.): 129$(M + 1)^+$, 111$(M + 1 - H_2O)^+$, 85$(C_4H_4O_2 + 1)^+$.

Elemental analysis:

Found : C 56.3%; H 6.27%.

Calculated for $C_6H_8O_3$: C 56.3%; H 6.25%.

This reaction was repeated under various conditions (Table XV and XVI) and results were listed in Table XV and XVI.

The preparation of 5-(1´-hydroxypropyl)-butenolide (137)

To a solution of dichloromethane (5ml) containing 0.314g (2mmol) of 2-trimethylsilyloxyfuran (101) and 0.128 (2.4mmol) of propanal, stannic chloride (2 drops) was added under an atmosphere of argon at -78°C with stirring. The reaction mixture was stirred (1 h), then quenched with water(-78°C) and warmed to RT. After the usual work-up, a light yellow oil(0.147g) was obtained and identified as the title compound (137) along with 0.036g of compound (99). The overall yield is 73% after correction for the recovery of (99). The ratio of threo / erythro is 81:19 by temperature programmed GLC analysis[programme:80°C(5min)--(5°C/min)--140°C--(20°/min)--200°C].

IR: ν_{max} 3440, 3100, 2860-2965, 1745, 1785, 1600 cm^{-1}

^{1}H-NMR :

Threo isomer: δ 7.56(1H, dd, J=6.0 and 1.5Hz, C-4), 6.15(1H, dd, J=6.0 and 2.0Hz, C-3), 5.1(1H, m, C-5), 3.74(1H m, C-6), 3.58(1H, br.s, OH), 1.60(2H, m , J=7.5Hz, C-7), 1.02 (3H, t, J=7.5 Hz, C-8).

Erythro isomer : δ 7.67(1H, dd, J=5.5 and 1.5Hz, C-4), 6.18(1H, dd, J=5.5 and 2.0 Hz, C-3), 4.99(1H, m, C-5), 3.75(1H, m, C-6), 3.58(1H, br.s, OH), 1.60(2H, m, C-7),

1.04(3H, t, J=7.5Hz, C-8).

^{13}C-NMR :

Threo isomer: δ 173.8(C=O, C-2), 154.9(C-4), 122.3 (C-3), 86.2(C-5), 72.6(C-6), 26.1(C-7), 10.1(C-8).

Erythro isomer: δ 173.7(C=O, C-2), 154.7(C-4), 122.3(C-3), 86.3(C-5), 72.7 (C-6), 26.3(C-7), 10.0(C-8).

MS(C.I.): 143$(M+1)^+$, 125$(M + 1 - H_2O)^+$, 85$(C_4H_4O_2 + 1)^+$.

Elemental Analysis:

Found : C 58.9%; H 6.92%.

Calculated for $C_7H_{10}O_3$: C 59.2%; H 7.05%.

Preparation of 5-(1'-hydroxyphenylmethyl)-butenolide(138)

To a solution of 2-trimethylsilyloxyfuran (101) (0.314,2mmol) and benzaldehyde (0.233g, 2.4 mmol) in DCM (5ml), stannic chloride (2 drops) was added under an atmosphere of argon at -78°C with stirring. The resulting mixture was stirred (-78°C,1h); and quenched with water. The solvent was evaporated in vacuo and the residue was extracted with ethyl acetate (40ml). After the usual work-up, a pale yellow oil (0.226g) was obtained and identified as the title compound (138) along with 0.017g of (99). The overall yield is 80%. The ratio threo/erythro is 88:12 via temperature-programmed GLC analysis [programme: 120°C(5min)--(5°C/min)--180°C--180 °C(10min)--(20°C/min)--240°C].

IR : ν_{max} 3430(OH), 3070, 1750(mix) cm^{-1}

^{1}H-NMR :

Threo isomer: δ 7.31-7.38(5H, m, Ar-H), 7.16(1H, dd, J=5.5 and 2.0 Hz, C-4), 6.07(1H, dd, J=5.5 and 2.0Hz, C-3), 5.15(1H, ddd, J=2.0, 2.0 and 7.0Hz, C-5), 4.69(1H, d, J=7.0Hz, C-6), 3.40(1H, br.s, OH).

Erythro isomer: δ 7.31-7.38(5H, m, Ar-H), 7.16(1H, dd, J= 6.0 and 2.0 Hz, C-4), 6.13(1H, dd, J= 6.0 and 2.0Hz, C-3), 5.16(1H, ddd, J=5.0, 2.0 and 2.0Hz, C-5), 5.06(1H, d, J=5.0 Hz, C-6), 3.26(1H, br.s, OH).

^{13}C-NMR :

Threo isomer: δ 173.2(C=O,C-2), 153.3(C-4), 128.8, 128.7, 126.7 and 126.0 (carbons of Ph), 122.8(C-3), 86.6(C-5), 75.3(C-6).

Erythro isomer: δ 173.7(C=O,C-2), 152.9(C-4), 128.7, 128.4, 126.3 and 126.0 (carbons of Ph), 123.1(C-3), 86.9(C-5), 72.9(C-6).

MS(C.I.): 191$(M + 1)^+$, 173$(M + 1 - H_2O)^+$, 107(side chain + 1)$^+$, 85$(M + 1 -$ side chain$)^+$.

Elemental analysis:

Found: C 69.7%; H 5.23%.

Caculated for $C_{11}H_{10}O_3$: C 69.5%; H 5.26%.

Preparation of 5-(1´-hydroxyhexyl)-butenolide (139)

Using the same experimental procedure with as described for the preparation of (116) and starting with (101)(20mmol) and

hexanal(24mmol), a pale yellow oil (2.83g, 77%) was obtained and identified as a pair of diastereoisomers of (139)(threo / erythro = 93:7). Pure threo isomer(m.p. 60.5°C) was isolated by crystallization from ether.

IR (threo isomer,nujol mull):

ν_{max} 3360(OH), 3090, 1720, 1595 cm^{-1}

^{1}H-NMR:

Threo isomer: δ 7.53(1H, dd, J=6.0 and 2.0Hz, C-4), 6.16(1H, dd, J=6.0 and 2.0Hz, 5.03(1H, dt, J=4.0 and 2.0Hz, C-5), 3.79(1H, m, C-6), 3.13(1H, br.s, OH), 1.56(3H, m, C-7 and C-8_A), 1.34(5H, m, C-8_B and C-9, C-10), 0.89(3H, t, J=6.5Hz, C-11).

Erythro isomer: δ 7.54(1H, dd, J=6.0 and 2.0Hz, C-4), 6.18(1H, dd, J=6.0 and 2.0Hz, C-3), 4.97(1H, m, C-5), 3.37(1H, m, C-6), 3.13(1H, br.s, OH), 1.58(3H, m, C-7 and C-8_A), 1.31(5H, m, C-8_B and C-9, C-10), 0.89(3H, t, J=6.5Hz, C-11).

^{13}C-NMR:

Threo isomer: δ 173.3(C-2), 154.4(C-4), 122.2(C-3), 86.2(C-5), 71.2(C-6), 32.9(C-9), 31.4(C-7), 25.1(C-8), 22.4 (C-10), 13.9(C-11).

Erythro isomer: δ 173.4(C-2), 154.1(C-4), 122.4(C-3), 86.3(C-5), 71.2(C-6), 32.9(C-9), 31.4(C-7), 24.8(C-8), 22.3 (C-10), 13.8(C-11).

MS(C.I.):185$(M + 1)^+$, 167$(M + 1 - H_2O)^+$, 84$(C_4H_4O_2)^+$

Elemental analysis:

Found : C 65.0%; H 8.68%.

Calculated for $C_{11}H_{16}O_3$: C 65.2%; H 8.75%.

Preparation of 5-(1´-hydroxy-2´-methylpropyl)-butenolide(140)

To a solution in DCM (5ml) of 2-trimethylsilyloxyfuran and 2-methylpropanal (0.18g,2.5mmol), stannic chloride (2 drops) was added under an atmosphere of argon at -78°C with stirring . The reaction mixture was stirred for one hour and quenched with water (-78°C) then warmed to room temperature and the solvent was evaporated under 45°C on a rotory evaporator. A light yellow oil (0.248g, 79.6%) was obtained and identified as the title compound (140) along with 0.019 g of (99). The overall yield is 91%. The ratio of threo / erythro is 94:6 by temperature programmed GLC analysis [programme:80°C(4min)--(5°C/min)--150°C(5min)--(20°C/min) -- 240°C(5min).]

IR : ν_{max} 3430(OH), 3100, 1740(C=O, mix), 1385, 1360cm^{-1}

^{1}H-NMR :

Threo isomer: δ 7.47 (1H, d,d, J=6.0 and 1.5Hz, C-4), 6.17(1H, dd, J=6.0 and 2.0Hz, C-3), 5.16(1H, ddd, J=4.5, 2.0 and 1.5Hz, C-5), 3.46(1H, dd, J=4.5 and 7Hz, C-6), 2.47(1H, br.s, OH), 1.94(1H, m, J=7Hz, C-7), 1.07(3H, d, J=7.0, C-8_1), 1.05(3H, d, J=7Hz, C-8_2).

Erythro isomer: δ 7.61(1H,dd,J=6and1.5Hz,C-4), 6.17(1H,

dd, J=6andl.5Hz,C-3), 5.08(1H,dt,J=7andl.5Hz,C-5), 3.48(1H,dd, J=7Hz,C-6), 2.47(1H,br.s,OH), 1.93(1H,m,J=7Hz,C-7), 1.04(3H,d, J=7Hz,C-8_1), 1.03(1H,d, J=7Hz,C-8_2).

^{13}C-NMR :

Threo isomer: δ 173(C=O), 154.4(C-4), 122.4(C-3), 84.6 (C-5), 76.4 (C-6), 31.6(C-7), 19.4, 17.8.

Erythro isomer: δ 154.3(C-4), 122.4(C-3), 84.6(C-5), 76.4(c-6), 30.9(C-7), 18.9(C-$8_{1,2}$).

MS(C.I.): 157$(M + 1)^+$, 139$(M + 1 - H_2O)^+$, 85$(C_4H_4O_2 + 1)^+$.

Elemental analysis:

Found: C 61.3% ; H 8.01%.

Calculated for $C_8H_{12}O_3$: C 61.5%; H 7.69%.

Preparation of 3-(1′-hydroxyethyl)-butenolide (130):

To a solution of 2-trimethylsilyloxyfuran (5ml of 1.6M of solution in pentane, 8 mmol) and ethanal (1.57g, 10mmol) in THF (15ml), a chloroform (0.3ml) solution of $Eu(fod)_3$ (46.7mg/ml) was added dropwise under an atmosphere of argon with stirring at the room temperature. After stirring (7 days, RT), the solvent was evaporated on a rotary evaporator under 30^{o}C. The residue was treated with dilute hydrochloric acid (1ml of 2N solution in 30ml of water) and the aqueous phase was washed with DCM (5ml X 2) before it was neutralized with aqueous sodium bicarbonate. After evaporation of the solvent , the residue was extracted with ethyl acetate (25ml) . The

organic phase was dried over magnesium sulphate and evaporated on a rotary evaporator under 35°C. After purification by short column chromatography (silica gel, DCM/EtOAc = 20:1 - 4:1), a yellow oil was isolated and identified as the title compound (130) from the following data, along with the recovery of the compound (99). The yield of (130)(68%) was determined via temperature programmed GLC analysis of the crude product using an internal standard and corrected for the recovery of (99).

IR : ν_{max} 3440(OH), 3100, 1730(C=O), 1375 cm^{-1}

^{1}H-NMR :

δ 7.37(1H, dt, J=1.5 and 3.0Hz, C-4), 4.88(2H, d, J=1.5Hz, C-5), 4.53(1H, br.s, C-1′), 3.31(1H, br.s, OH), 1.41(3H, d, J=6.0Hz, C-2′).

^{13}C-NMR :

δ 173.2(C=O, C-2′), 145.2(C-4), 136.0(C-3), 70.8(C-5), 63.2(C-1′), 21.9(C-2′).

MS: m/e= 128 $(M)^{+\cdot}$, 111$(M - OH)^{+\cdot}$, 84$(C_4H_4O_2)^{+\cdot}$.

Elemental analysis:

Found: C 56.1%; H 6.32%.

Calculated for $C_6H_8O_3$: C 56.3%; H 6.25%.

Preparation of 3-(1′-hydroxypropyl)-butenolide (131):

To a solution of 2-trimethylsilyloxyfuran (10ml of 1.6M solution in pentane, 16mmol) and propanal (1.28g, 24mmol) in

THF (25ml), a chloroform (0.5ml) solution of $Eu(fod)_3$ (46.7mg/ml) was added dropwise under an atmosphere of argon with stirring at room temperature. The reaction mixture was heated and stirred for 72 hours at 40°C before the solvent was evaporated on a rotary evaporator under 30°C. The residue was treated with dilute hydrochloric acid (2N) and extracted with ethyl acetate (3 X 20 ml). After the usual work-up, the title compound (131) was obtained as a yellowish oil along with (99) and the dehydration product (132), and some uncharacterized by-products. After temperature programmed GLC analysis of the crude product using an internal standard sample and corrected for the recovery of (99), the yield of (131) is 54.3% and the yield of (132) is 21% .

The data on the title compound (131) are as below:

IR : ν_{max} 3450(OH), 3090, 1725(C=O), 1375 cm^{-1}

^{1}H-NMR :

δ 7.38(1H, dt, J=3.0 and 1.5Hz, C-4), 4.86(2H, dd, J=1.5 and 2.0Hz, C-5), 4.46(1H, br.m, C-1′), 3.20(1H, s, OH), 1.71(2H, m, J=14 and 7Hz, C-2′), 0.99(3H, t, J=7Hz, C-3′).

^{13}C-NMR :

δ 173.2(C=O, C-2), 145.3(C-4), 136.2(C-3), 70.4(C-5), 68.0(C-1′), 28.3(C-2′), 9.4(C-3′).

MS(C.I.): 143$(M + 1)^+$, 125$(M + 1 - H_2O)^+$, 85$(C_4H_4O_2 + 1)^+$.

Elemental analysis:

Found: C 59.5%; H 6.99%.

Calculated for $C_7H_{10}O_3$: C 59.2%; H 7.05%.

The data on the dehydration product 3-(prop-1´-enyl)-butenolide (132) is as below:

IR : ν_{max} 3120, 2850 - 2960, 1780, 1750, 1370 cm^{-1}

^{1}H-NMR :

δ 7.13(1H, m, J=2.0Hz, C-4), 6.81 (1H, m, J=16.0, 7.0 and 1.5Hz, C-1´), 6.15(1H, m, J=16.0 and 1.5Hz, C-2´), 4.80 (2H, dd, J=2.0 and 1.5Hz, C-5), 1.82(3H, dd, J=8.0 and 1.5Hz, C-3´).

MS: m/e=124$(M)^{+\cdot}$, 95$(M - C_2H_5)^{+\cdot}$, 79$(M - CHO_2)^{+\cdot}$, 67$(92 - CO)^{+\cdot}$.

[The sample was further purified by preparative TLC chromatography (5mm thin silica gel plate with concentrated zone, pet. ether / ethyl acetate = 4:1, 3 times).]

The preparation of 3-(1´-hydroxy-2´-methylpropyl)-butenolide (133) :

To a solution of 2-trimethylsilyloxyfuran (10ml of 1.6M solution in pentane, 16mmol) and 2-methyl-propanal (1.8g, 25mmol) in THF (25ml), was added dropwise a chloroform (0.5ml) solution of $Eu(fod)_3$ (46.7mg/ml) under an atmosphere of argon with stirring at room temperature. The reaction mixture was heated and stirred (48 h, 60°C) before the solvent was evaporated in vacuo (< 30°C). The residue was treated with

dilute hydrochloric acid (2N) and extracted with ethyl acetate (3 X 20ml), After the usual work-up, the major component as a pale yellow oil was isolated and identified as the title compound (133) along with some uncharacterized by-products.

After temperature programmed GLC analysis of the crude product using an internal standard and corrected for the recovery of (99), the yield of (133) is 65% .

IR : ν_{max} 3450(OH), 3100, 1730(C=O), 1380, 1365 cm^{-1}

^{1}H-NMR :

δ 7.38 (1H, dd, J= 1.5 and 4.0Hz, C-4), 4.65 (2H, dd, J=1.5 and 1.0Hz, C-5), 4.30 (1H, br.d, J=5.5, C-1′), 3.00 (1H, br.s, OH), 2.08 (1H, m, C-2′), 0.94 (6H, dd, J=7.0 and 9.5Hz, C-3′).

^{13}C-NMR :

δ 173.3 (C=O, C-2), 146 (C-4), 135.3 (C-3), 72.0(C-5), 70.5 (C-1′), 32.1 (C-2′), 18.9(C-3$_1$′), 16.5 (C-3$_2$′).

MS(C.I.): 157$(M + 1)^+$, 139$(M + 1 - H_2O)^+$.

Elemental analysis : Found : C 61.3%; H 7.85%.

Calculated for $C_8H_{12}O_3$: C 61.5%; H 7.69%.

The preparation of 3-(1′-hydroxybenzyl)-butenolide (134):

To a solution of 2-trimethylsilyloxyfuran (10ml of 1.6M solution in pentane, 16 mmol) and benzaldehyde (2ml, about 20 mmol) in THF (25ml), a chloroform (0.5ml) solution of $Eu(fod)_3$ (46.7mg/ml) was added dropwise under an atmosphere

of argon with stirring at room temperature. The reaction mixture was heated up and stirred for 48 hours at 67°C before the solvent was evaporated on a rotary evaporator under 40°C. The residue was treated with dilute hydrochloric acid (2N) and extracted three times with ethyl acetate (3 X 20 ml). After being worked up as normal, a yellowish oil was obtained as the major component and identified as the title compound (134) along with (99) and some uncharacterized by-products. After temperature-programmed GLC analysis of crude product using an internal standard and corrected for the recovery of (99), the overall yield of (134) is 73%. None of 5-substituted product was detected

IR : ν_{max} 3430(OH), 3070, 1740(C=O) cm^{-1}

^{1}H-NMR :

δ 7.28 -7.39 (5H, m, Ar-H), 7.17 (1H, dt, J= 2.0 and 1.5Hz, C-4), 5.51 (1H, d, J=2.0Hz, C-1′), 4.72 (2H, d, J=1.5Hz, C-5), 3.72 (1H, br.s, OH).

^{13}C-NMR :

δ 173.1 (C=O, C-2), 146.4 (C-4), 140.3 (C-3), 136.3 (C-2′), 128.6 (C-3′ and C-7′), 128.2 (C-5′), 126.5 (C-4′ and C-6′), 70.7 (C-5), 69.0 (C-1′).

MS: m/e=190$(M)^{+\cdot}$, 172$(M - H_2O)^{+\cdot}$, 144$(172 - CO)^{+\cdot}$, 108(side chain)$^{+\cdot}$.

Elemental analysis :

Found: C 69.2%; H 5.53%.

Calculated for $C_{11}H_{10}O_3$: C 69.5%; H 5.26%.

Preparation of threo 4,5-dihydroxydecanoic acid γ-lactone (141) via hydrogenation of (139)[68]

The threo diastereoisomer of (139) in EtOAc (20ml) was treated with 10% Pd on carbon catalyst (0.0268g). After usual work-up as described before, the desired (141) was obtained as a clear crystalline solid (0.21g, >95%) which melted at hand temperature.

IR ($CHCl_3$ solution): ν_{max} 3400(OH), 1760(C=O) cm^{-1}

^{1}H-NMR:

Threo isomer: δ 4.42(1H, dt, J=7.5 and 4.5Hz, C-5), 3.57 (1H, m, C-6), 2.82(1H, br.s, OH), 2.55(2H, m, C-3), 2.19(2H, m, C-3), 1.58(3H, m, $C\text{-}7_A$ and C-8), 1.31(5H, m, $C\text{-}7_B$ and C-8, C-9), 0.89(3H, t, J=6.5Hz, C-10).

^{13}C-NMR:

Threo isomer: δ 177.6(C-2), 83.0(C-5), 73.2(C-6), 32.7, 31.5, 28.6, 25.0, 23.9, 22.4, 13.8 (aliphatic carbons).

MS (C.I.): $187(M + 1)^+$, $169(M + 1 - H_2O)^+$

Elemental analysis: Found: C 64.5%; H 19.1%.

$C_{11}H_{18}O_3$ requires: C 64.7; H 19.0.

Preparation of 5-(1′-oxycarbamidoethyl)-butenolide(142)

To a solution of 5-(1′-hydroxyethyl)-butenolide (136)(3.8g, 29.7mmol) in DCM (20ml), was added dropwise a 2.85ml of (chlorosulfonyl isocyanate (CSI)(32.7mmol) under an atmosphere of argon with stirring (-78°C). The reaction was carried out

at -78°C for 6 hours until no starting material (136) could be detected from TLC(silica gel, pet. ether/EtOAc = 2:3). The solvent was evaporated in vacuo (<30°C) and the semi-solid residue was hydrolyzed with an aqueous solution of saturated sodium metabisulphite (10ml) at 0°C. After being stirred for a further hour, it was extracted with EtOAc (20ml X 3), washed with diluted aqueous sodium bicarbonate then brine, dried over $MgSO_4$, concentrated in vacuo. The desired compound (142) (3.5g, 69%) was obtained as a slightly yellow solid and was further purified by crystallization from EtOAc and pet. ether.

^{1}H-NMR(acetone-d_6 solution):

Threo isomer: δ 7.62(1H, dd, J=6 and 1.5Hz, C-4), 6.16(1H, dd, J=6 and 2Hz, C-3), 5.98(2H, br.s, NH_2), 5.19 (1H, m, C-5), 5.06(1H, m, C-6), 1.32(3H, d, J=6.5Hz, C-7).

Erythro isomer: δ 7.76(1H, dd, J=6 and 1.5Hz, C-4), 6.22(1H, dd, J=6 and 2Hz, C-3), 5.98(2H, br.s, NH_2), 5.22 (1H, m, C-5), 5.04(1H, m, C-6), 1.19(1H, d, J=6.5Hz, C-7).

^{13}C-NMR(acetone-d_6):

Threo isomer: δ 206.4(C-9), 173.2(C-2), 155.0(C-4), 122.7(C-7), 85.5(C-5), 68.8(C-6), 17.0(C-7).

Erythro isomer: δ 206.3(C-9), 173.4(C-2), 154.5(C-4), 122.9(C-3), 85.2(C-5), 69.7(C-6), 15.1(C-7).

MS (C.I.): 172$(M + 1)^+$, 129$(M + 1 - CHNO)^+$, 111(129 - $OH)^+$, 84$(C_2H_4O_2)^+$.

The Diels-Alder reaction between (132) and Cookson's reagent

To a solution of dienelactone (132)(49.6mg, 4mmol) in $CHCl_3$

(10ml), was added a solution of Cookson's reagent (1.1 equiv.) in $CHCl_3$ dropwise whilst stirring at 0°C until the red colour of reagent was changed. After one more hour stirring at RT, the resulting mixture was concentrated in vacuo (<35°C) and purified by flash chromatography (silica gel, EtOAc/pet. ether = 1:3 to 1:1). A white solid (Rf=0.33, pet. ether/EtOAc=2:1) (m.p.163-164°C, ratio=6:1, 89mg, 94%) was obtained and identified as the compound (143) from following data:

^{1}H-NMR:

Major isomer: δ 1.48(3H, d, J=7Hz, C-8), 4.36(1H, t, J=9Hz, C-5_A), 4.60(1H, m, J=9 and 6Hz, C-4), 4.92(1H, m, J=7 and 3.5Hz, C-7), 4.99(1H, t, J=9Hz, C-5_B), 6.92(1H, t, J=3.5Hz, C-6), 7.49(5H, m, CH of Ph).

Minor isomer: δ 1.80(3H, d, J=7Hz, C-8), 4.38(1H, dd, J=9Hz, C-5_A), 4.62(1H, m, C-4), 4.92(1H, m, C-7), 4.99(1H, t, J=9Hz, C-5_B), 6.87(1H, t, J=3Hz, C-6), 7.41(5H, m, CH of Ph).

^{13}C-NMR:

Major isomer: δ 165.8(C=O), 155.0(C-6), 150.3(C_1 of Ph), 135.6(C-3), 129.3, 128.6, 125.2(carbons of Ph), 69.3(C-5), 54.7 (C-4), 50.0(C-7), 17.0(C-8).

MS: m/e=299$(M)^{+\cdot}$, 222$(M - C_6H_5)^{+\cdot}$.

Elemental analysis: Found: C 60.5%; H 4.05%; N 14.1%

Calculated for $C_{15}H_{13}N_3O_4$: C 60.2%; H 4.34% ; N 14.3%.

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PART TWO

Diastereoselective Synthesis of 1-Amino-1-Cyclopropane-Carboxylic Acid Derivatives

INTRODUCTION TO

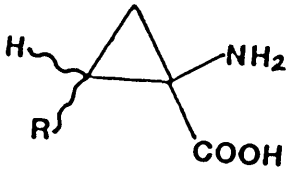
PART TWO

Chapter 1: A brief review of some previous work on the synthesis of ACPC derivatives

1-1. Background

During the last few years, increasing attention has been paid to the synthesis and study of 1-amino-1-cyclopropane-carboxylic acids because of their proven and potential biological activities[1-11]. Some ten of these amino acids have been isolated from various microorganisms and higher plants[1c, 12-14], 1-amino-1-cyclopropane carboxylic acid (ACPC) itself being an intermediate in the biosynthesis of ethylene, a phytohormone that initiates fruit ripening and regulates many aspects of plant growth and development[13]. Also cis-1-amino-2-ethyl cyclopropane carboxylic acid (coronamic acid) is a main constituent of coronatine, a toxin produced by Ps. coronofacines[1c]. In recent years the possible value of "cyclopropylogs" of the essential amino acids (ACPC) in which the C_α-C_β bond forms one side of the three-membered ring (1) has been recognized by several workers [3, 15-18].

This structural feature restricts rotation about the C_α-C_β bond so that any β-functionality is fixed in space with respect to the amine and acid moieties as occurs in dehydroamino acid (ACPC) residues, but the cyclopropane ring



(1)

re-introduces chirality into the system. Steric hindrance to reactions at carbonyl group is expected to be intermediate between that of the α-alkyl and α,α-dialkyl amino acids, so that insertion into a peptide sequence should give amide bonds resistant to hydrolysis. Also, the pseudo conjugation of carboxyl functions with the cyclopropyl-group may lead to reactivity which is of value in the synthesis of enzyme inhibitors[3,17,18] . Very recently, in fact, it has been shown that the natural unsubstituted compound (1, R=H) reacts readily with a pyridoxal-dependent enzyme, giving α-oxo -butyrate and ammonia[19]. It has also recently been incorporated into peptide derivatives[20, 21].

Because alkyl and aryl-substituted cyclopropyl amino acids are potentially important analogues of the natural amino acids, and because no diastereoselective route to them is available, we have investigated the asymmetric synthesis of 2-substituted -1-amino-1-cyclopropane carboxylic acids. As we are facing two problems, asymmetric synthesis of amino acids as well as cyclopropanation, it is necessary to briefly review some previous work on the synthesis of 1-amino-1-cyclopropane carboxylic acids (ACPC).

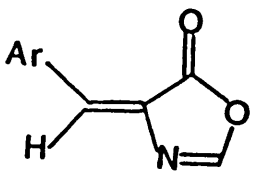
Several routes so far have been developed for the synthesis of ACPC derivatives. The methods can be grouped into two main categories: (A) Syntheses based on glycine derivatives and glycine related derivatives; (B) Syntheses from non-amino acid compounds as summarized in Schemes 1 and 2 and these can be further subdivided into five parts according to the type of reactions and starting compounds.

1-2. Carbene insertion into a dehydroamino acid.

1-2-1 Burger route

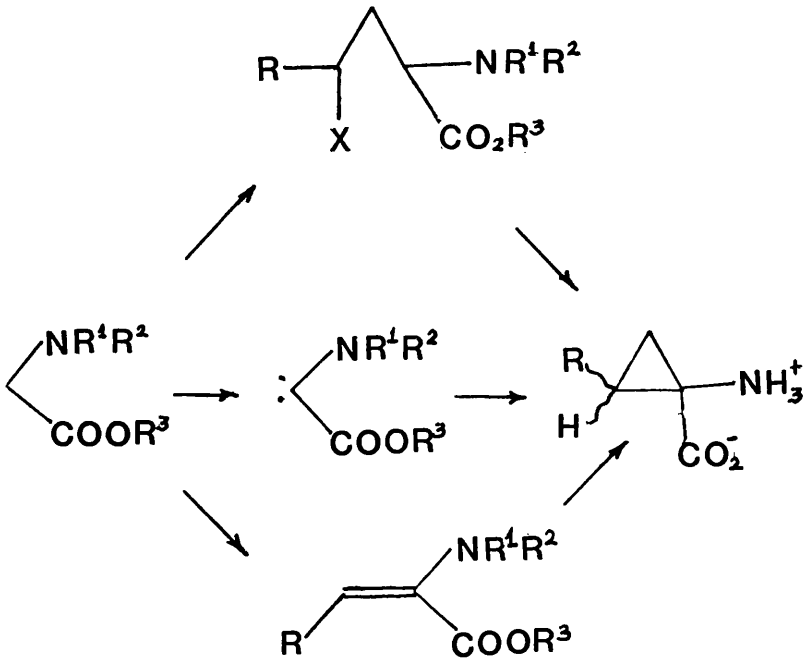
This route was first developed in Burger's laboratory[17]. Burger's reagent (2) was used as a key intermediate to form a cyclopropane ring via a carbene generated from diazomethane.

(2)

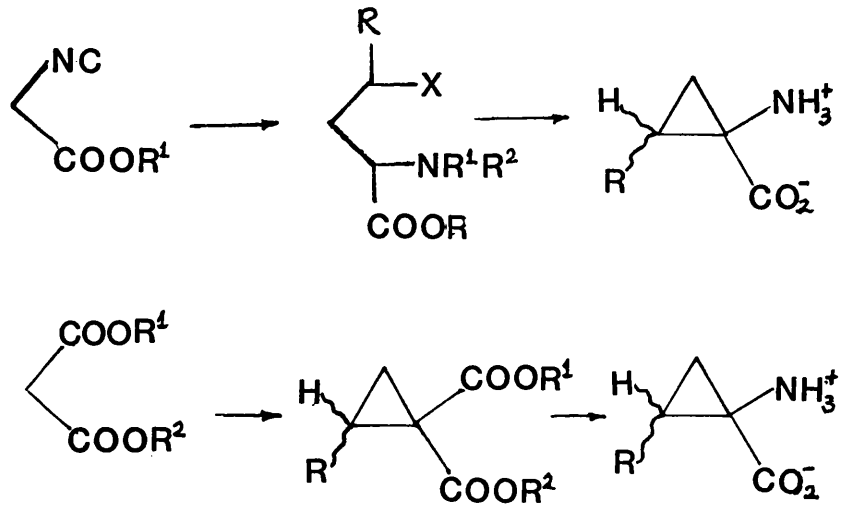


The route is shown in Scheme 3.

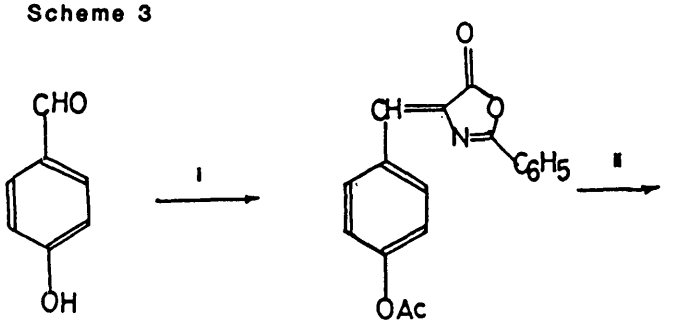
Scheme 1



Scheme 2



Scheme 3



(3) (4) (5) (6)

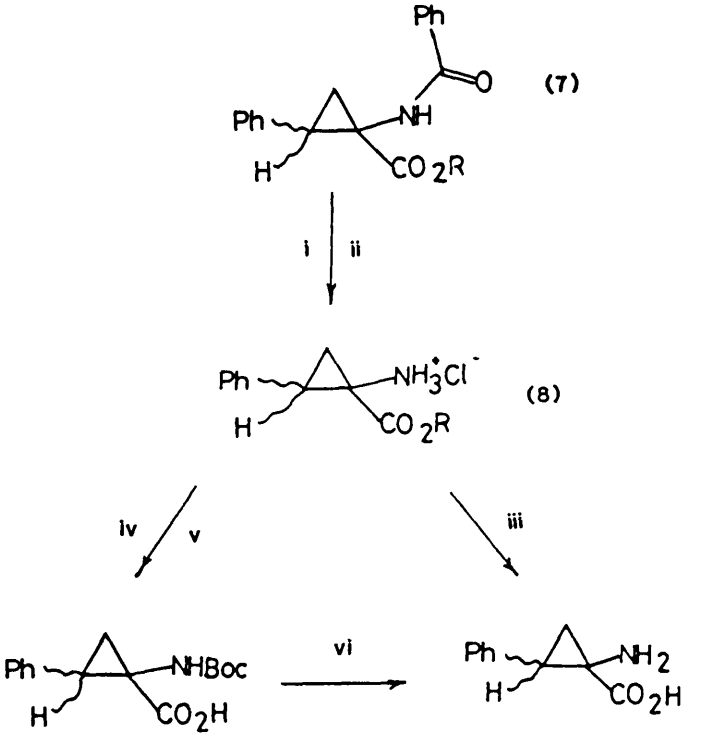
Reagent :

i) Hippuric acid, MeCOONa (anhydrous)/Ac_2O;

ii) CH_2N_2 ;

iii) a) NaOH ; b) H^+/ H_2O.

Scheme 4



Reagent :

i. $Et_3^+OBF_4^-$; ii. H^+/ H_2O ; iii. H_2 / Pd ;

iv. $(Boc)_2O$; v. OH^- ; vi. HCl / EtOAc .

Condensation of the aromatic aldehyde (3) with hippuric acid produces the unsaturated azlactone (4) which is subsequently treated with diazomethane to yield (5).The complete hydrolysis of (5) using the methods developed by Stammer[22] (Scheme 4) and Bernabe (Scheme 5)[23] gives the free amino acid. A series of ACPC derivatives have been made by applying this method (Scheme 6) [17, 24-26].

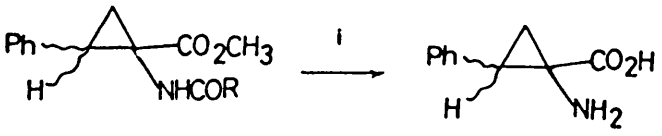
The main disadvantages of the approach were (a) the difficulty experienced in the hydrolysis to the free amino acid[22,23] because there were several competitive side reactions, (b) the low yield , and (c) the non-chiral nature of the synthesis.

1-2-2. Stammer modified method

Efforts to solve these problems[27-30], culminated in a simpler and more attractive procedure developed by Stammer et al[27] for the synthesis of certain racemic ACPC derivatives . The intermediate dehydroalanine derivatives (12) were obtained by dehydration[28] of the corresponding serine derivatives in good yield (Scheme 7).

Treatment of (12) with various diazo-compounds in cold ether solution gave the pyrazolines (13). Pyrolysis of these at 90^0C in toluene followed by hydrolysis of the reaction products (14), gave the N-Boc-cyclopropyl amino acids in good yield.

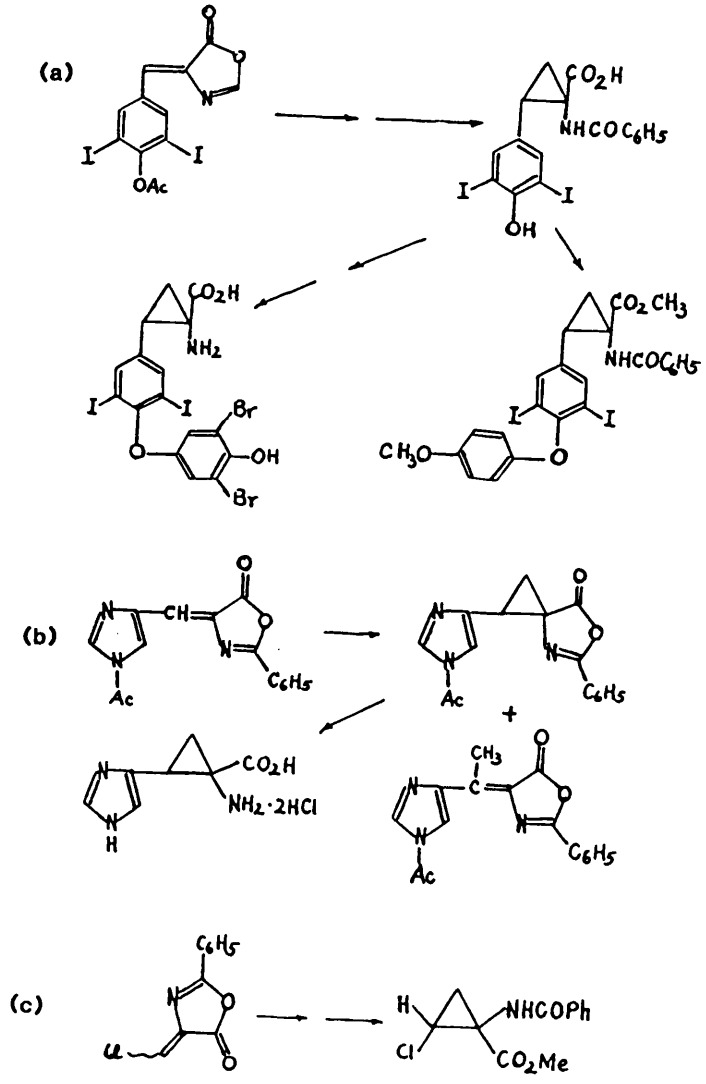
Scheme 5



Reagent :

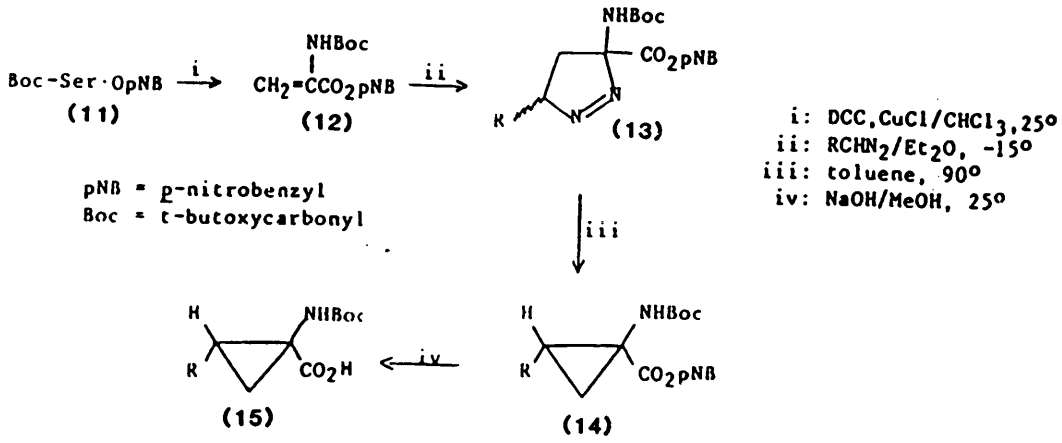
i. HCl / AcOH, reflux .

Scheme 6



either isomer
E(27%) or Z(18%).

Scheme 7

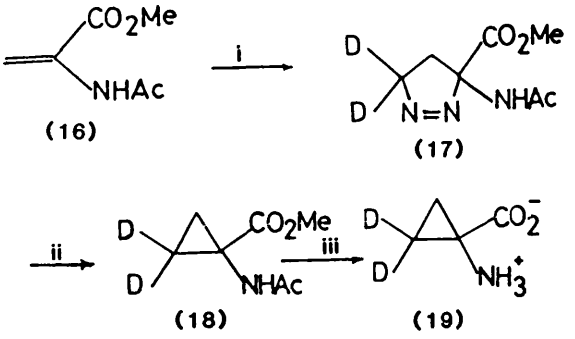


1-2-3. Other syntheses using the same approach as described above

The same approach has been used[31] to prepare the dideuterio ACPC (19) shown in Scheme 8 and the glutamic acid and arginine analogues (25) and (30)[33-35] in Scheme 9.

The last compound is the natural product carnosadine and in its synthesis, the key intermediate (21) (Scheme 9), was prepared according to Erlenmeyer's method[34, 35]. The cyclopropane ring was constructed by thermal or photochemical degradation of a pyrazoline intermediate (22). The methoxycarbonyl group of the product (23) was then converted into an amino group by the Hofmann reaction. The pair of racemic compounds (26) were then separated by a classical resolution method and each diastereoisomer was converted into optically active carnosadine (30).

Scheme 8

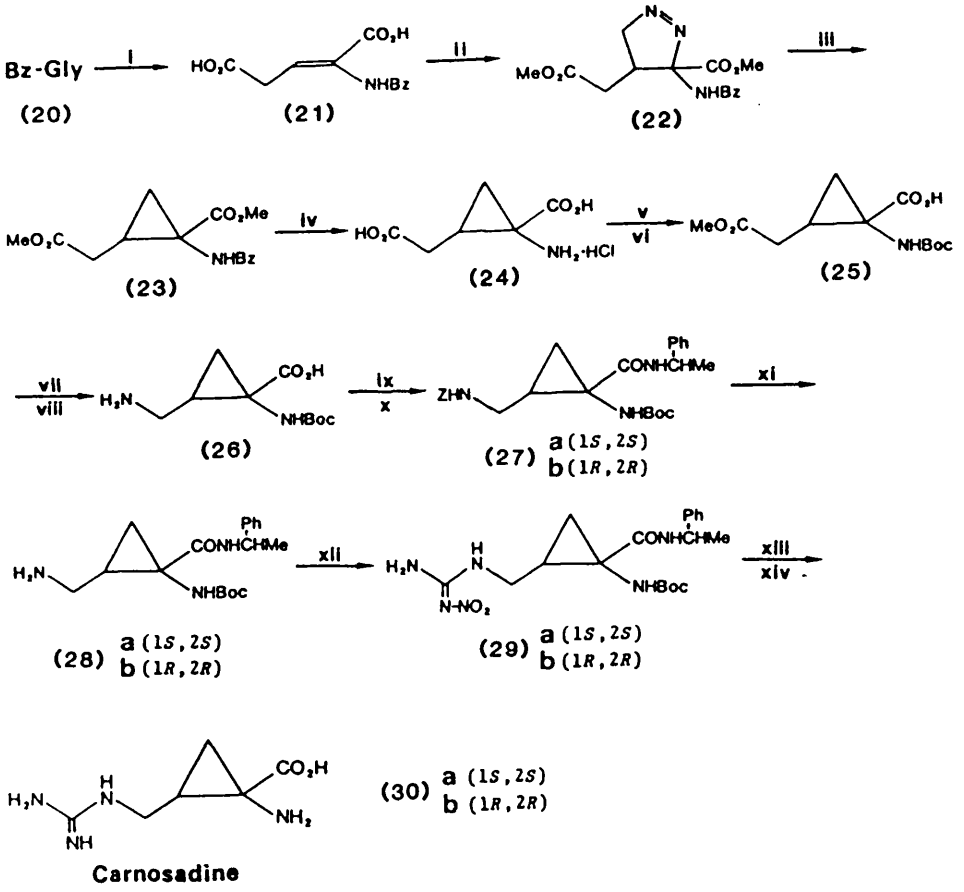


Reagent :

i. CD_2N_2 ; ii. heat ;

iii. HCl / H_2O .

Scheme 9



Carnosadine

Scheme 9. i)Ref. 6; ii)CH_2N_2, MeOH, quant.; iii)(a)hv(high pressure mercury arc), toluene, 78%, (b)reflux, toluene, 71%; iv)reflux, 6M HCl, 95%; v)2M HCl/MeOH, 84%; vi)di-*t*-butyl dicarbonate (Boc_2O), $NaHCO_3$, 83%; vii)liq. NH_3/MeOH, 94%; viii)3M NaOH, Br_2, 73%; ix)benzyloxycarbonyl chloride (Z-Cl), 1M NaOH, quant.; x)(*R*)-(+)-α-methylbenzylamine, *N,N'*-dicyclohexylcarbodiimide—1-hydroxybenzotriazole(DCC-HOBt), THF, 82%; xi)H_2, Pd black, MeOH, 92%(28a), 94%(28b); xii)3,5-dimethyl-1-nitroguanylpyrazole, MeOH, 72%(29a), 59%(29b); xiii)H_2, Pd black, MeOH; xiv)reflux, 6M HCl, 63%(30a), 59%(30b) as 2HCl salt from 29a and 29b, respectively.

1-3. A masked glycine derived carbene insertion into an alkene

In contrast with Berger's route, a significant method has been developed by Schollkopf et al[36] which involves the generation of a glycine carbene followed by asymmetric addition to a vinyl compound (Scheme 10).

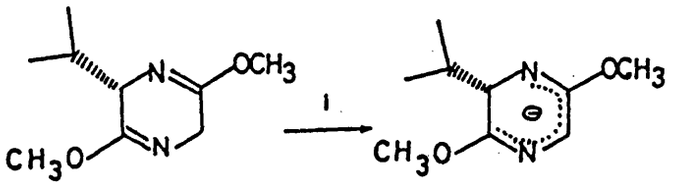
Schollkopf's reagent (31) was prepared from the cyclization of glycine and valine [37] and the key intermediate (35) was achieved, in the case of the lithiated bislactim ether (32) of cyclo(L-Val-Gly-), by a diazo-group transfer reaction[38] which was carried out with tosyl azide. After generation of the carbene (36) by treating (35) with a second equivalent of n-butyl lithium and loss of one equivalent of dilithium tosylamide in the presence of cyclohexane, a good yield of (71%) of spiro compound (37) was obtained in the diastereomeric ratio of 49:1. This was subsequently hydrolyzed to (38) and (39) in yields of 43% and 38% respectively. The advantage of this approach is its diastereoselectivity, but it is a very expensive route and has limitations[39].

1-4. Internal S_N1 Cyclopropanation

1-4-1. Non-chiral syntheses

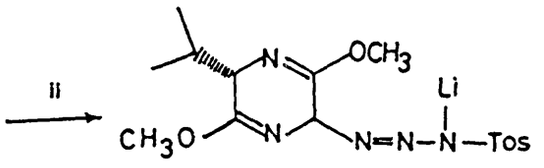
Niemann and his collegues are the pioneers, so far, in this area[40]. 1-Acetamido-1-carbethoxy cyclopropane (41) has been

Scheme 10



(31)

(32)



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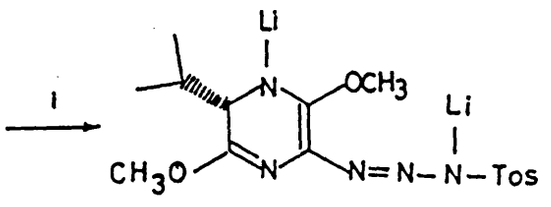

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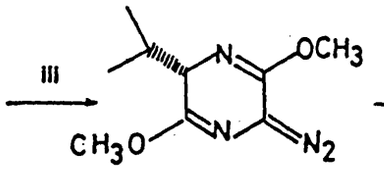

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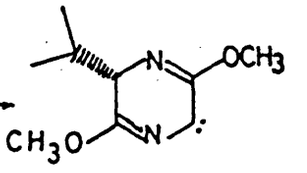

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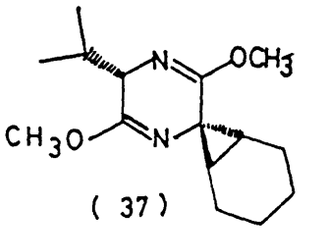

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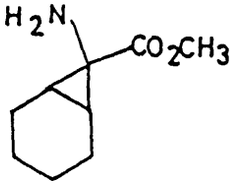
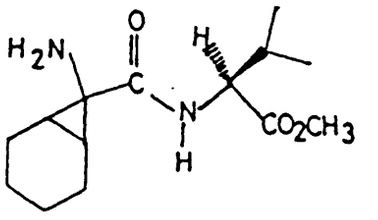


(38)



(39)

Reagent :

i. n-Butyl lithium; ii. Tos-N_3; iii. N_2/ heat;

iv. cyclohexene; v. H^+/ H_2O .

prepared by the thermal decomposition of the quaternary base derived from the methiodide of diethyl N,N-dimethyl-aminoethylacetamidomalonate (40). This appears to be the first example of the synthesis of a cyclopropane ring through exhaustive methylation (Scheme 11).

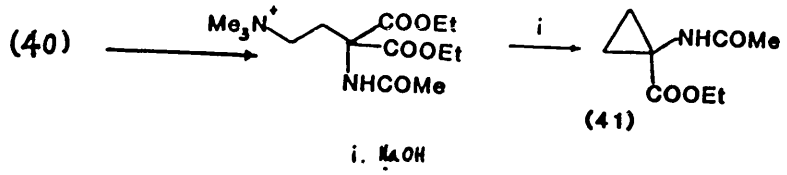
Alternatively, Rich et al[41] used N-t-butoxycarbonyl methionine methyl ester, Boc-Met-OMe(42) as the starting compound (Scheme 12), which was converted to the sulfonium salt (43) by reaction with methyl fluorosulfonate in chloroform[42].

Treatment of (43) with silver oxide/methyl iodide in DMF gave the N-methylaminocyclopropane-1-carboxylic acid derivative (44) which was the expected product based on the reaction of acetyl methionine with these reagents[43].

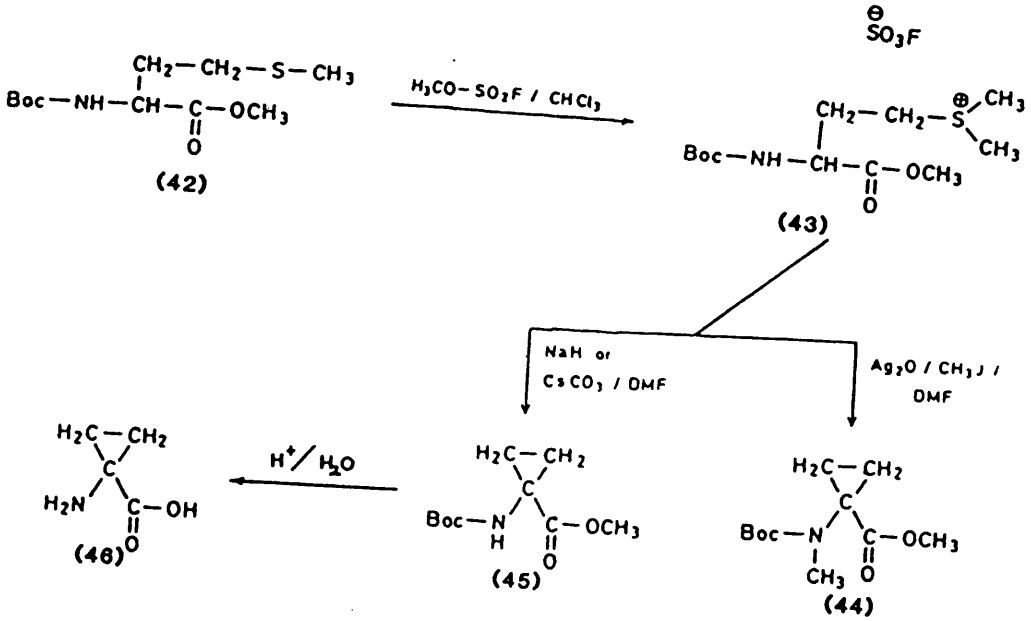
Reaction of the sulfonium salt (43) with either sodium hydride or caesium carbonate (but not tertiary amines) in DMF gave the cyclopropane derivatives (45) in 70-72% yield after crystallization. After acid hydrolysis, the free amino acid (46) is obtained in 84% yield.

In comparison, Tamm and his colleagues chose cleverly the N-carbobenzyloxy-L-glutamic acid α-methyl ester (47) as a precursor (Scheme 13)[44] which is converted into the bromoderivative (48) and subsequent β-elimination by the use

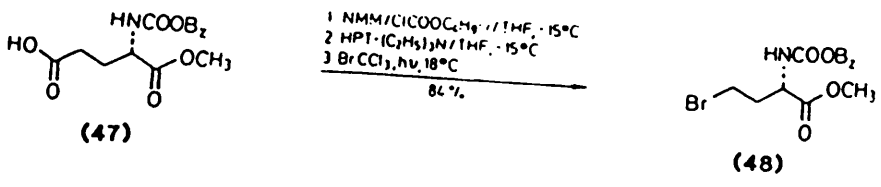
Scheme 11:

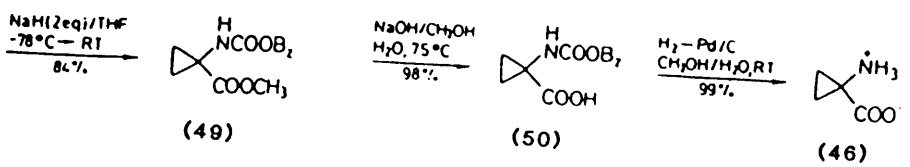


Scheme 12



Scheme 13



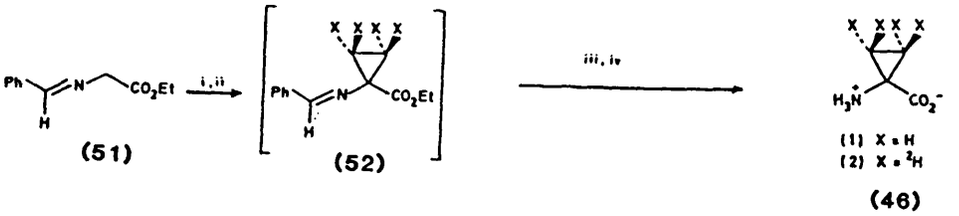


Bz = Benzyl
HPT = *N*-Hydroxypyridin-2-thion
NMM = *N*-Methylmorpholin

of sodium hydride leads to the fully protected intermediate(49) in good yield. Deprotection by sodium hydroxide and hydrogenolysis yields almost quantitively the key substance (46) .

Baldwin[45] and his colleagues have also worked in this area. They used ethyl 2-benzyl imino acetate (51) as starting compound. After being treated with LDA and an alkyl dihalide, the desired product (46) was obtained in the overall yield of 28% (Scheme 14).

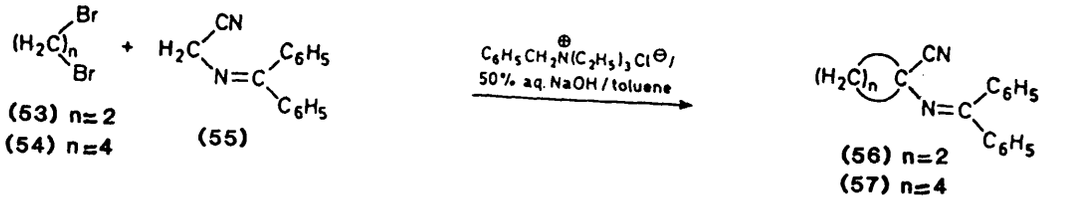
Scheme 14



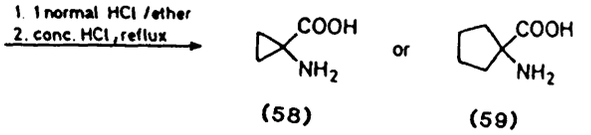
(51) (52) (1) X = H (2) X = ^{2}H (46)

Reagents and conditions: i, Pr^i_2NLi (2.6 equiv.), tetrahydrofuran, hexamethylphosphoramide, −65 °C; ii, $C_2D_2Br_4$; iii, 6 M HCl, heat; iv, Dowex 50W - X 8(H), recrystallisation (H_2O–EtOH).

Scheme 15



(53) n=2 (54) n=4 (55) (56) n=2 (57) n=4



(58) (59)

Instead of using (51), another interesting method has been developed by O´Donnell et al.[46, 47-50] (Scheme 15).

The starting protected glycine intermediate(55) was prepared in 93% yield from aminoacetonitrile hydrochloride and benzophenone imine by a trans-imination procedure[51]. Substrate (55) was readily dialkylated by (53) or (54), in a single step,using a catalytic phase-transfer procedure[52] with benzyl-triethyl ammonium chloride, and toluene, followed by acidic hydrolysis, giving (58) in 87% overall yield.

The advantage of this route is the high yield, but unfortunately it still belongs to the class of non-chiral syntheses.

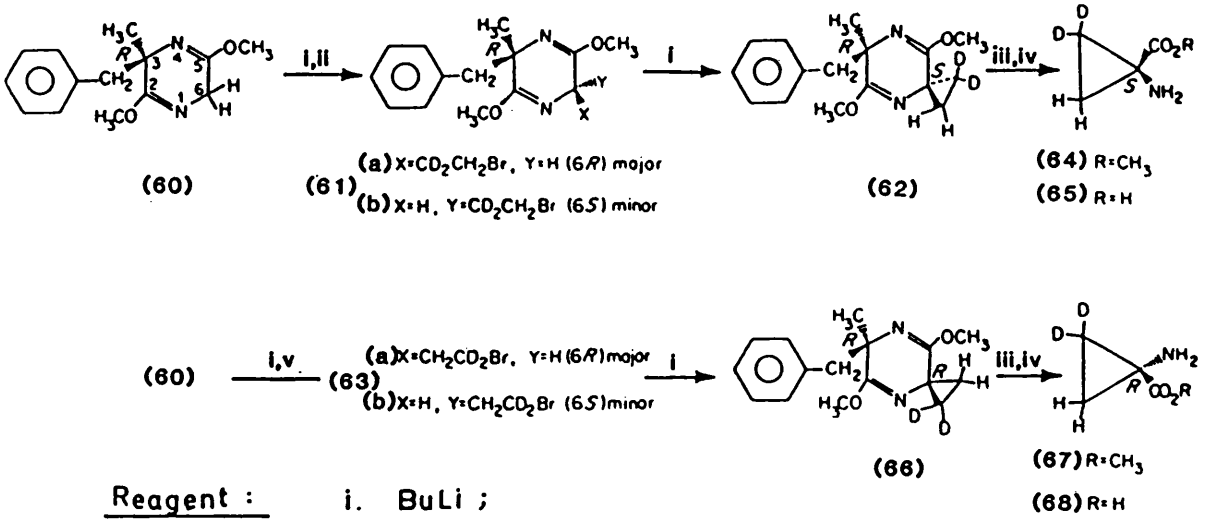
1-4-2. Asymmetric route

As for asymmetric routes, Woodard´s synthesis (Scheme 16)[53] is the only example so far found. He chose significantly the chiral reagent R-(+)-2-methyl-3-phenylalanine (60) as a starting material. This was prepared from phenyl acetone[54] in a convenient four-step sequence in 49% overall yield by a modified asymmetric Strecker synthesis[55] which was first described by Weinges and co-workers[56].

The synthesis of the cyclo(methyl- Phe-Gly) began with the esterification of the phenylalanine derivative with methanolic

HCl[57] and the resulting methyl ester was condensed[58] with N-t-Boc-glycine to give the dipeptide methyl ester. Following the procedure of Nitecki[59], the dipeptide methyl ester was cyclized, after treating with formic acid by boiling in a mixture of sec-butanol and toluene (2:1) to yield the 2,5-diketopiperazine. The piperazine was then converted into

Scheme 16



the bislactim ether (60) by treatment with trimethyloxonium tetrafluoroborate[60]. The advantage of this approach is that, in contrast to Schollkopf's reagent (31), the chiral reagent (60) lacks an α-hydrogen and therefore it can only be alkylated at the C-6 position. Further there is no possibility of aromatization under aldol reaction conditions. The diastereoselectivity and yields are very high. Another very interesting discovery is the phenomenon of the anti-Schollkopf

products in the cases of reaction with deuterated bromoethyl triflates to give (61) and (63), where the approach of the electrophile mainly takes place Syn to the bulky 3-benzyl group, in contrast to the more usual way in which the approach of the electrophile is trans to the bulky 3-benzyl group.

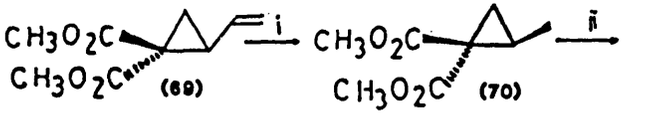
1-5. Synthesis from cyclopropane malonate.

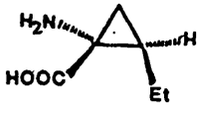
This area has been fully explored by many workers. The pioneering work appears to have been done by Japanese researchers[61b] (Scheme 17).

The dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (69) was prepared by condensation of trans-1,4-dibromo-2-butene and dimethyl malonate according to a known procedure[62]. After reduction of the vinyl double bond in (69) which was accomplished by tosyl hydrazide in diglyme[63], selective amination of one of the carboxy groups[64], Hoffmann degradation[65] of (71), and subsequent hydrolysis of resultant carbamate ester (72), the desired compound (73) was obtained in racemic form.

Recent synthetic endeavours around this area have been conducted by Walsh and Baldwin. The racemic vinyl, methyl, and ethyl compounds,(the latter in deuterated form), were prepared by Walsh[66] (Schemes 18 and 19).

Scheme 17



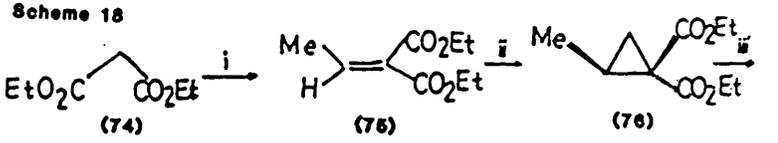


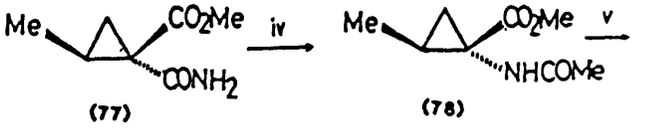
(73) d,l- coronamic acid

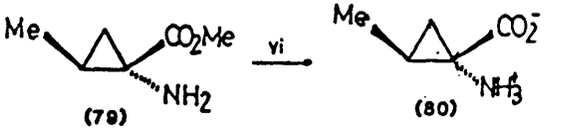
Reagents :

i) Tosyl hydrazide/diglyme; ii) NH_3/MeOH;
iii) Br_2 / NaOH - MeOH ; iv) OH^-/ H_2O .

Scheme 18



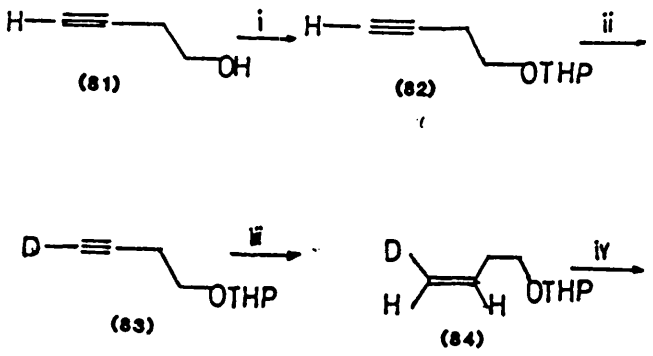


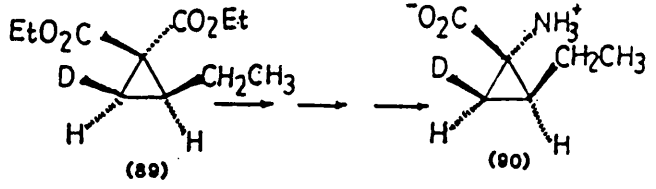


Reagents :

i) CH_3CHO / Ac_2O ; ii) $Me_3S^+O\ I^-$/ NaH / DMSO;
iii) NH_3/ MeOH / NaOMe; iv) Br_2/ NaOMe / MeOH ;
v) TMSI / $CDCl_3$; vi) (a) NaOH (1N) ;
(b) TMSI / O_2S  .

Scheme 19





Reagents :

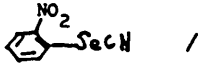
i)  / $POCl_3$;

ii) (a) n-BuLi ; (b) D_2O ;

iii) lindlar catalyst / quinoline / H_2 ;

iv) (a) Me_2S_2 / SO_2Cl_2; (b) $NaCH(CO_2Et)_2$;
(c) $(MeO)_2SO_2$; (d) NaOEt ;

v) Pyr^+OTs^- / MeOH ;

vi)  / Bu_3P ;

vii) (a) H_2O_2 ; (b) Δ

viii) $TsNHNH_2$ / diglyme .

The key intermediate in these syntheses is a malonate which is selectively aminated at its less-hindered carbonyl group to provide an amide which is subjected to Hoffmann degradation. This route ultimately affords analogues with syn stereochemistry of the alkyl substituent relative to the carbonyl group. These compounds were used in the studies of the Pseudomonas enzyme ACPC deaminase which, interestingly, has stereochemical requirements opposite to those for ethylene biosynthesis.

Baldwin[67] has recently modified Walsh's route to provide the correct relative stereochemistry for methyl and ethyl analogues in ethylene biosynthesis. This involves first hydrolyzing the cyclopropyl malonate and then executing an amination / Curtius degradation sequence. Baldwin has also prepared deuterated analogues using this methodology and has resolved and assigned absolute configurations to these products. This paper reports a much more direct method for preparing those analogues which are useful for ethylene biosynthesis studies. It includes the first synthesis of such compounds from materials of unambiguous absolute configuration and provides hard evidence concerning the steric requirements of the active center for ethylene production.

1-6. Others

1-6-1 Synthesis from 1-isocyano-1-carboxylate derivatives.

Two routes so far have been found in this area, both of which were first developed [68,69,70] in Schollkopf's laboratory. In the early 1970's, ethyl 1-isocyano-cyclopropane 1,1-carboxylates were employed as starting materials to synthesize ACPC derivatives[68]. One of the very interesting ways is the cyclopropanation via Michael addition (Scheme 20)

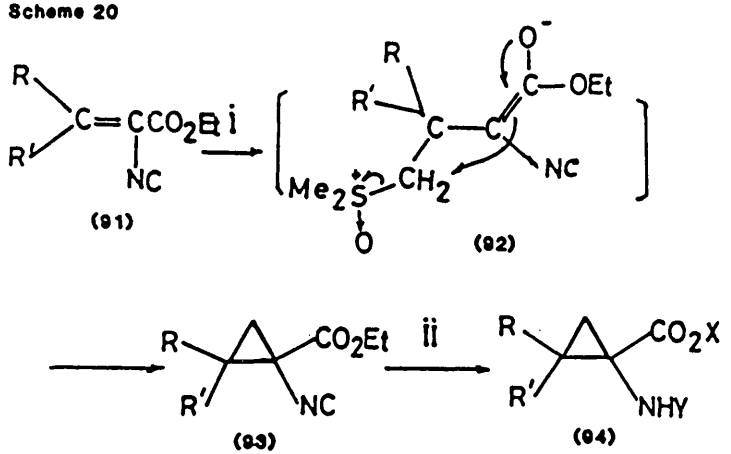
The useful intermediate (91) was obtained by the aldol condensation of ethyl 2-isocyanoacetate with various carbonyl compounds. After treating with the normal sulfur ylide reagent (from trimethyloxo sulphonium salt) products (93) were obtained in good yield which subsequently were hydrolyzed to ACPC (94) via either acidic or basic conditions.

Compound (93) (when R = R' = H) was also prepared by cycloalkylation of ethyl 2-isocyanoacetate (95) with (96) in the presence of NaH (Scheme 21).

The advantage for these approaches is the simplicity of synthesis and the good yield, but it has no chiral control and two pairs of enantiomers (when R is different to R') were generated at the same time.

In order to solve these problems, Schollkopf employed some chiral epoxides (104) as alkylating reagents[69](Scheme 22).

Scheme 20



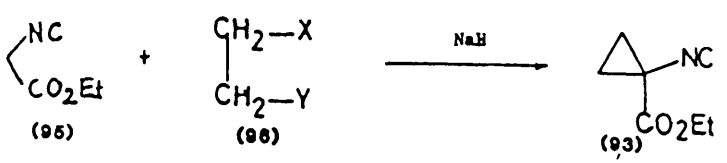
R=H, Me, Et, $CHMe_2$, Ph
R'=H, Me, Et, Ph
RR'=-$(CH_2)_5$-

X= Et, H
Y= N-formyl, H

Reagents:

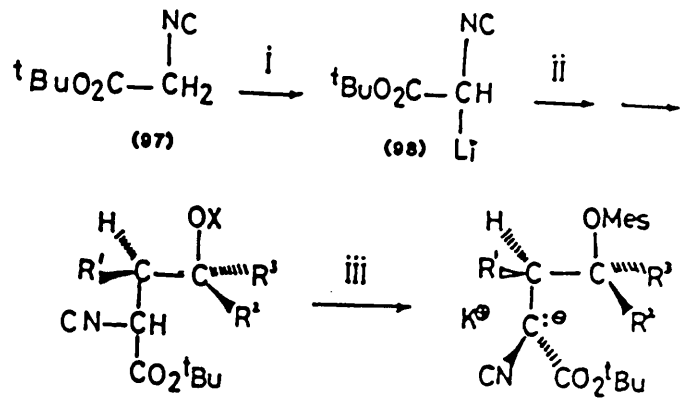
i) $Me_2\overset{O}{\overset{\|}{S}}{}^{+}-CH_2^-$; ii) a) H^+ / H_2O ; b) OH^- .

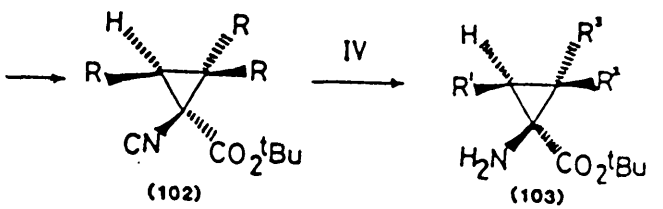
Scheme 21

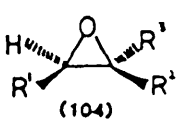


(a) X = Y = Br
(b) X = Cl, Y = 4-$MeC_6H_4SO_3CH_2CH_2Cl$

Scheme 22







Reagents:

i) BuLi ;
ii) a) (&) ; b) BF_3OEt_2;
iii) KO^tBu ;
iv) HCl (conc.)/ H_2O, Δ .

(a) R^1=R^2=R^3= H
(b) R^1= R^3= H, R^2= CH_3
(c) R^1= R^3= H, R^2= C_2H_5
(d) R^1= R^3=-CH_3, R^2= H
(e) R^1= R^2= -$(CH_2)_4$-, R^3= H

The starting material (97) was prepared from t-butyl N-formyl glycinate[71] by elimination of water according to the method of Ugi et al.[72]. The lithiated ester (98) reacts with epoxides (104) in the presence of boron trifluoride etherate[73] to give the t-butyl 4-hydroxy-2-isocyano alkanoates (99). The substitution takes place with inversion of configuration at the the less hindered carbon of the epoxides. The compounds (99) are then mesylated to compound (100) which readily undergo base-induced cyclization to the t-butyl 1-isocyano-1-cyclo propane carboxylates (101) with high diastereoselectivity. The advantage of this method is the good yield and the simplicity of the conversion of the isocyano-t-butyl esters (102) into amino acids (103).

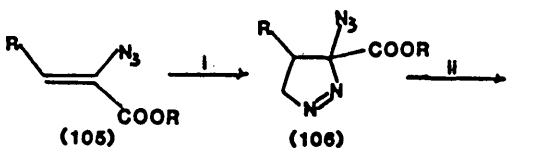
Apart from Schollkopf, Pirrung et al[74,75,61a] synthesized some ACPCs from methyl i-isocyano acetate and chiral 1,2-dibromo alkane.

1-6-2 Synthesis via 2-azido-2-alkenoates

Besides malonate derivatives, the use of 2-azido-2-alkenoates has been explored by many workers[76, 77](Scheme 23).

The title compounds (107) are logical precursors of 1-amino cyclopropane carboxylic acids which were readily prepared by the cycloaddition of diazomethane to 2-azido-2-alkenoates (105) and subsequent selective thermal decomposition of the resulting pyrazoline derivatives (106).

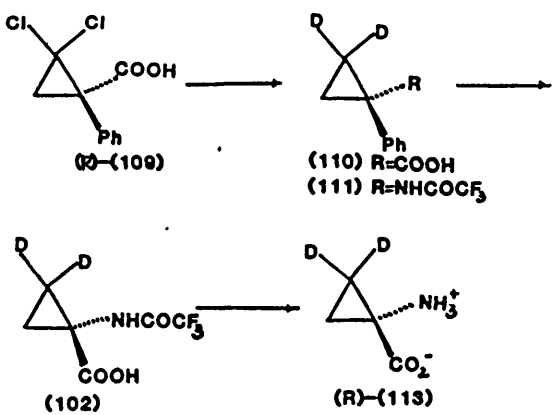
Scheme 23



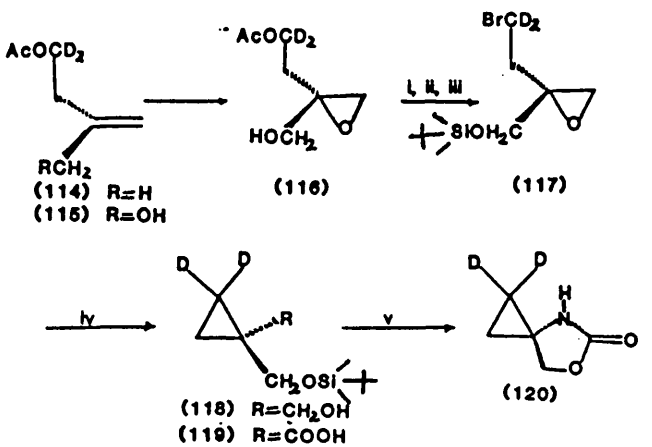
Reagents:

I CH_2N_2 II Δ,CCl_4 III H_2–Pd/C,MeOH

Scheme 24



Scheme 25



Reagents:

I OH^- II TsCl III Bu_4NBr IV LiI/THF V) RuO_4

1-6-3. The Georgia and Zurich synthesis

Two interesting routes have been developed independently[78] in Georgia and Zurich towards the synthesis of (106) .

The Georgia synthesis (Scheme 24) began with 2,2-dichloro 1-phenyl-cyclopropane carboxylic acid[79] (99) which ws resolved with (+)- or (-)-α-methylbenzylamine to give the pure antipodes.

Reduction of (R)-(109) methyl ester with 2.5 equiv of tri-n-butyltin deuteride gave, after hydrolysis, the deuterated acid (R)-(110), Curtius rearrangement of (110) led to the amine, purified as the crystalline trifluoroacetamide (111). Oxidation of (111) with RuO_4 afforded the acid (R)-(112) which was hydrolyzed to (R)-(113).

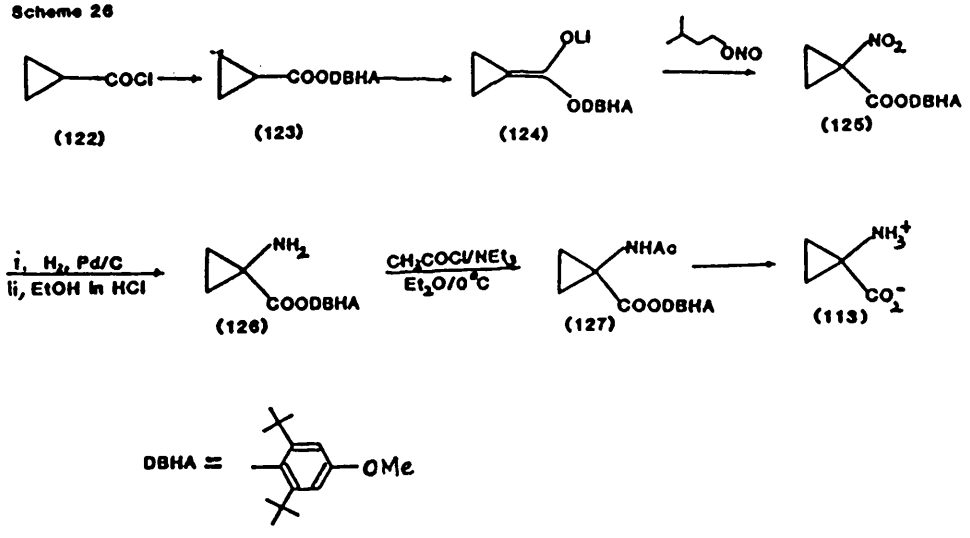
In the Zurich synthesis (Scheme 25), acetate (114), prepared from 3-methyl 3-butenoic acid by $LiAlD_4$ reduction followed by acetylation, was oxidized by SeO_2 and tert-butyl hydroperoxide to alcohol (115), separated from its concommitantly formed regioisomer by chromatography. Sharpless epoxidation[80] converted (115) to the (S)-epoxide (116). The tert-butyl dimethylsilyl ether of (116) was converted in three steps into bromide (117). The critical C-C bond was generated by an intramolecular displacement reaction when (117) was treated with lithium in THF to give the cyclopropane derivative (118). Oxidation of (118) with RuO_4 to acid (119)

and Curtius rearrangement of the latter furnished the oxazolidone (120), which was converted by hydrolysis, trifluoroacetylation, and chromic acid oxidation to amide (112), which was subsequently hydrolyzed to (R)-(-)-(113).

1-6-4. The Seebach route

Seebach also developed a route for the synthesis of (113)[81] (Scheme 26).

Scheme 26



The desired compound is synthesized from 2,6-di-tert-butyl -4-methoxyphenyl cyclopropane carboxylate (123) by an overall electrophilic amination. The key step is the nitration of the highly reactive enolate (124) generated by deprotonation of ester (123) with tert-butyl lithium.

RESULTS AND DISCUSSION FOR PART TWO

Chapter 2 : Cyclopropanation via addition-elimination reactions

2-1 Initial Plan

As seen in Chapter One , 1-amino-1-cyclopropane carboxylic acids have recently received an increasing amount of attention. There are two immediate reasons for incorporating them, in place of the corresponding natural amino acids, into biologically important small peptides:

(a) They may induce higher resistance to acid and enzyme degradation due to steric inhibition of hydrolysis since the cyclopropyl methylene group impedes approach of the incoming nucleophile along the 45^{o} approach vector from behind the amide carbonyl bond.

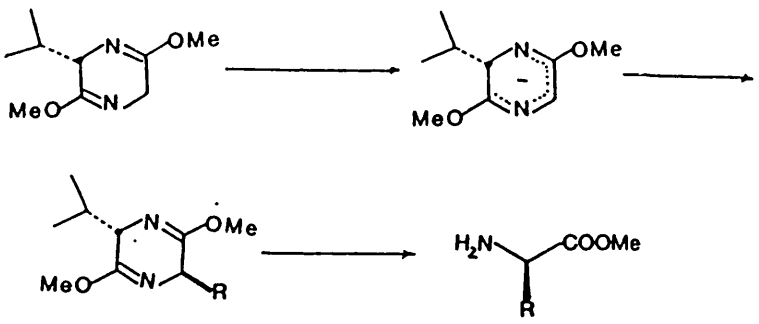
(b) Conformational restrictions in the peptides will result. If one of the cyclopropyl amino acid diastereoisomers resembles a conformation adopted by the natural substrate, then the reduced degrees of freedom would, at a receptor site, result in the accrual of entropic advantage with resultant increased binding .

Since no totally diastereoselective and general route has appeared in the literature, asymmetric synthetic routes are needed in order to satisfy the increasing demands of new peptide research .

Schollkopf has recently developed methodology[37] for

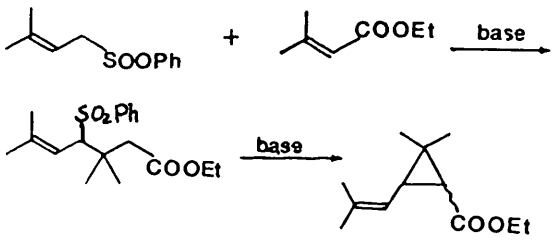
asymmetric syntheses of amino acids via alkylation of bis lactim ethers (Scheme 27)

Scheme 27



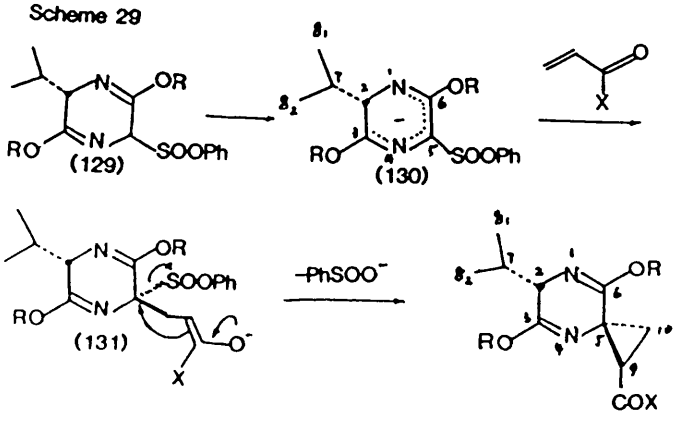
and Martel et al[82] have developed a method for the syntheses of chrysanthemic acid by an addition-elimination reaction (Scheme 28), thus

Scheme 28



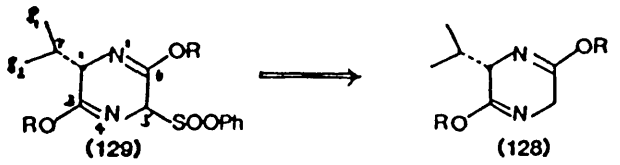
the possibility presented itself to us of combining the two strategies for the purpose of asymmetric syntheses of ACPCs (Scheme 29).

Scheme 29

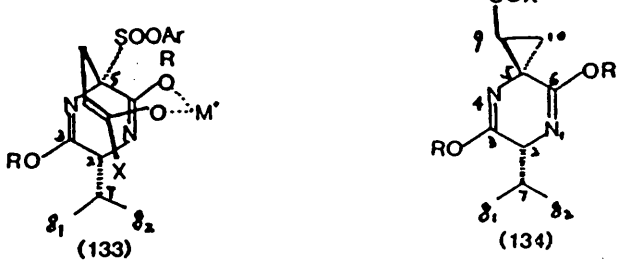


It was proposed that the sulfonyl derivatives (129) would be

prepared directly or indirectly from the Schollkopf reagent (128).



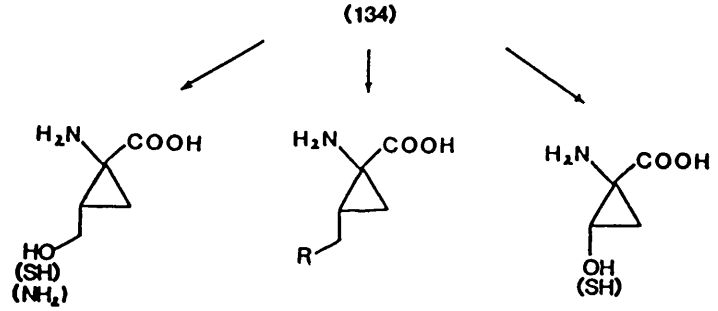
Michael addition[83] of the derived carbanion (130) would possibly proceed with α,β-unsaturated carbonyls to give enolates (131) which might cyclize with displacement of the tertiary sulphonate[84] to give the cyclopropanes (132). Whereas the absolute stereochemistry at C-5 may be predicted [82, 84], the emerging stereochemistry at C-9 needs to be determined.



Precise geometrical coordinates for adducts related to (129) are now available[83, 86]. It is therefore possible to construct, by molecular modelling, the enolate adduct (133) and to align the enolate for optimal overlap of the appropriate enolate p_z orbital with the departing RSO_2^- sp^3 rear orbital, and to demonstrate, theoretically, that in a beautifully-aligned metal ion bridged transition state (133) chelation control should lead unambiguously to a precisely predicted diastereoisomer (134). Utilizing the known coordinates for a lithium chelate (O-O, 2.8A; O-Li, 1.9A)

[87], a model energes in which there are minimal steric interactions anywhere in the molecule, particularly when X=H in (133). Note that non-ideal geometries are apparent for the other possible chelating combinations, i.e. with N(1) or with OR(6). A potentially stable early transition state model involving chelation control is therefore predictable.

The carbomethoxy group may potentially be modified to give a variety of substituted ACPCs as indicated below:



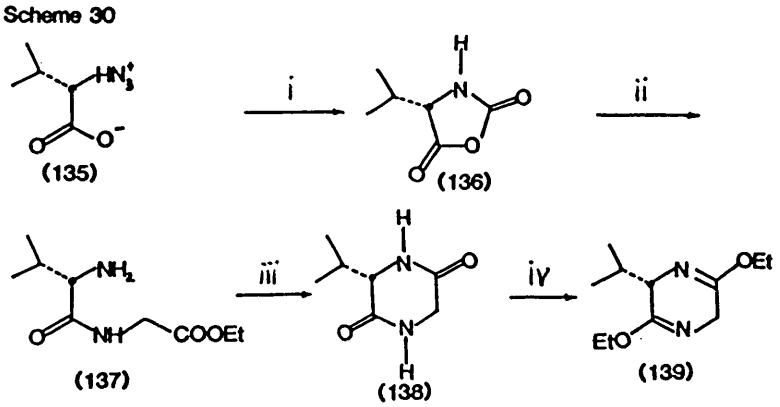
2-2 The Preparation of Schollkopf's reagent (128).

As the Schollkopf reagent is not readily available and also very expensive the programme started with the preparation of the bislactim ethers[85](Scheme 30)

The first step was carried out following Schollkopf's procedure, but instead of using gaseous phosgene, 20% phosgene in toluene was used. Experimental results showed that the reaction of L-valine in THF with phosgene solution in toluene went very slowly when molar equivalents of reactants were used and there was always a side reaction in which the

cleavage of THF by HCl took place. However, when 2.5 molar equiv. of phosgene solution in toluene and THF were used under 40^0C, nearly quantitive yield of the desired compound was achieved. The bis-lactam was prepared in 84% yield using Schollkopf's methodology.

Scheme 30



i) $COCl_2$ (20 % in toluene), THF ;

ii) Et_3N + $NH_2CH_2CO_2Et$-HCl, THF / $CHCl_3$;

iii) Toluene , reflux ;

iv) Et_3^+-BF_4^- , CH_2Cl_2 .

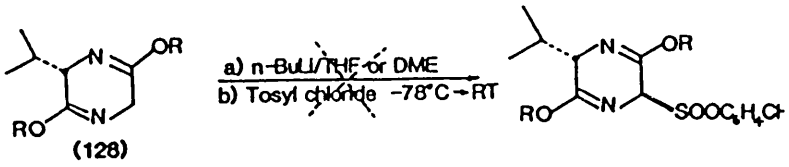
The etherification reaction was carried out (45%) at room temperature under argon using, as reagent, triethyloxonium tetrafluroborate which was prepared by a standard method[93].

2-3 Preparation of (2R)-2,5-dihydro-3,6-diethoxy-2-isopropyl -5-phenylsulphonylpyrazine (129)

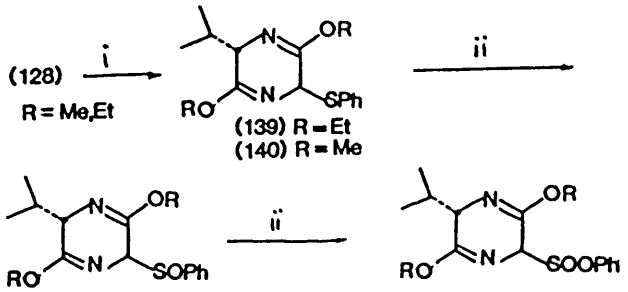
The C-sulphonylation of bislactim ether, Scheme 31 and Scheme

32, was investigated.

Scheme 31



Scheme 32

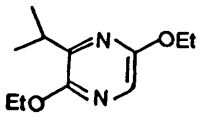


i) n-BuLi , THF, -78°C, phenyldisulfide.

ii) mCPBA (2.2 equivalents) in DCM from -78°C to RT

Although we were unaware of any precedent for direct C-tosylation of a carbanion, we attempted the reaction of (128) with tosyl chloride (Scheme 31). This was unsuccessful. No desired C-sulphonyl could be detected and only a small amount of starting bislactim ether were recovered along with some aromatized product (141) and uncharacterized polymers.

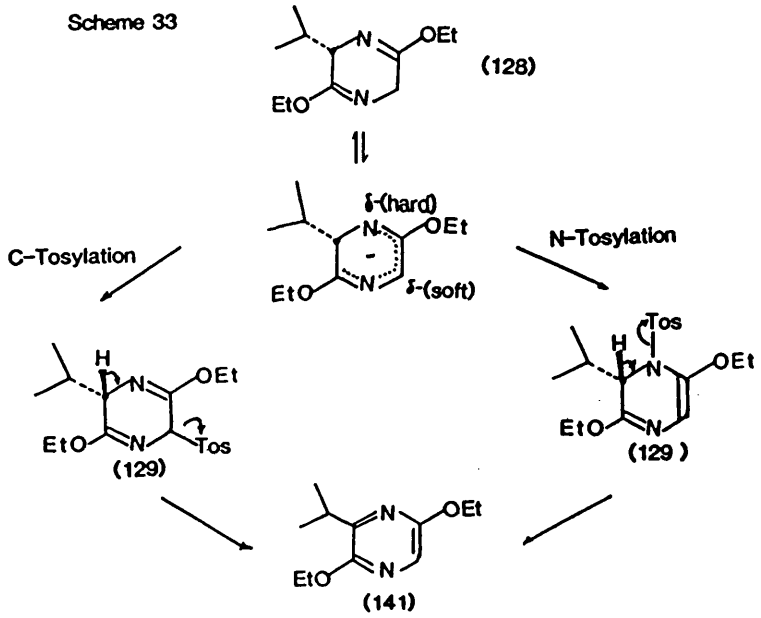
The structure of (141) was confirmed by spectroscopic considerations: Mass spectrum of this compound give $M^{+\cdot}$=210, corresponding to the formula $C_{11}H_{18}N_2O_2$. The IR spectrum has aromatic absorptions (ν_{max}3035cm^{-1}), but no absorption at 1685cm^{-1}(RO-C=N, of bislactim ether). The



(141)

chemical shift in its ^{1}H-NMR spectrum, δ 7.52ppm(1H,s) corresponds to the C-H in the aromatic system, and δ 3.30ppm(1H,septet) and 1.23ppm(6H,d) showed that the compound contains the (=CY-CHMe$_2$) fragment in accord with the structure(141). The formation of (141) could be accounted for in one or both of the following ways (Scheme 33) involving alternative modes of elimination of toluene sulphinic acid.

Scheme 33



An alternative way was then explored, involving the formation of the sulphide (139) followed by oxidation to the sulphonyl compound. The first step, making the carbanion at -78^{o}C (n-BuLi, THF), then quenching it with a THF solution of diphenyl disulphide[88], was investigated and the results are shown in Table 1.

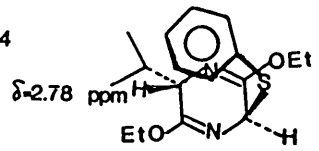
Table I

No.	R	Reaction conditions	Reaction products		
			Yield (%)	Ratio of Cis/Trans	No.
1	Me	-78°C (4hr), quenched with NH_4Cl-H_2O at -78°C	5		(40)
2	Et	-78°C to RT (4hr), quenched with NH_4Cl-H_2O at RT	78	1:5	(39)
3	Et	-78°C to RT (6hr), quenched with NH_4Cl-H_2O at RT	95	1:3	(39)
4	Me	-78°C to RT (7hr), quenched with NH_4Cl-H_2O at RT	96	2:3	(90)
5	Me	-78°C to RT (6hr), quenched with NH_4Cl-H_2O at -78°C	93	3:5	(90)

These assignments were made by reference to the shielding of the C_2-H proton which appears at 2.78 ppm in one diastereoisomer and at 3.85 ppm in the other. The assumption was made that this proton is strongly shielded in the trans-isomer by the -SPh benzene nucleus to which it bears a

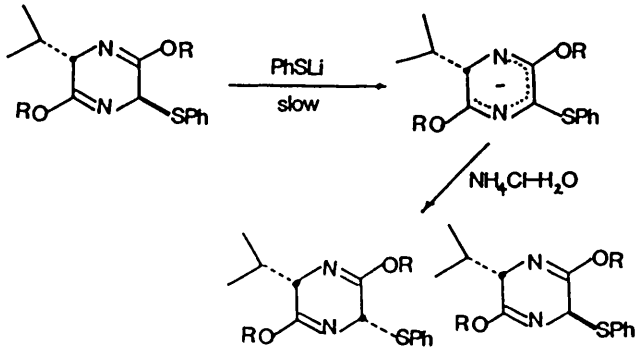
cis relationship. The C_2-H value in the parent ether (128) is 3.96 ppm.(Scheme 34)

Scheme 34



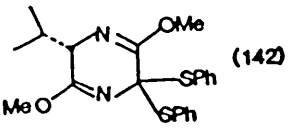
It appears from Table 1 that shorter reaction times favors the trans-isomer suggesting that this is the kinetically controlled product. The lower selectivity observed with longer reaction times indicates that equilibration occurs possibly via proton abstraction by PhS^-, so that the poorer selectivity reflects the small difference in energy between the two bislactim ethers. Thiophenolate anion is a much stronger base in THF than in aqueous media (Scheme 35).

Scheme 35



At this stage, the chirality at C-5 is unimportant[90], therefore no particular effort was made to increase the diastereoselectivity of the reaction.

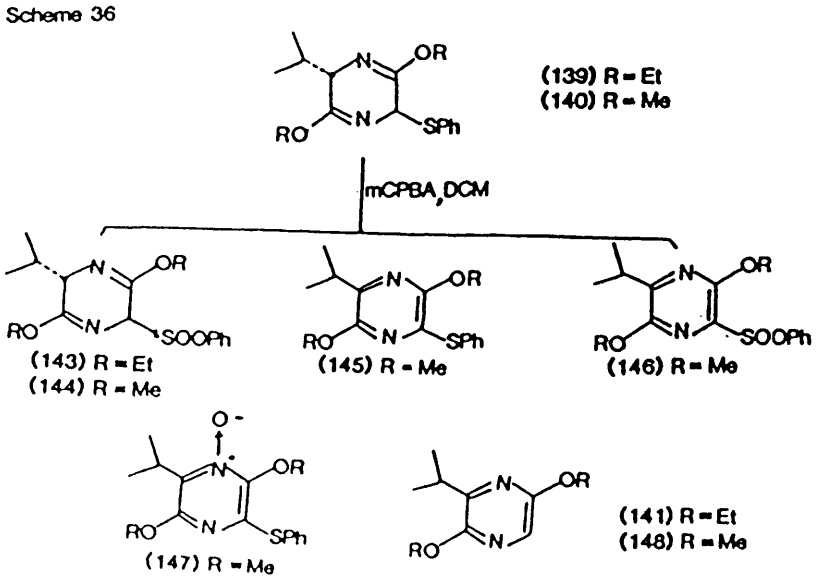
The spectral data for a side product (5%) in this stage closely resembled those for (140) except that the proton at δ5.15-5.30 ppm due to the C(5)-H is no longer present and the molecular weight ($M^{+\cdot}$, 401) shows the presence of an extra C_6H_5S- group. This indicates the structure shown as (142).



(142)

Conversion of sulphide (139) or (140) to (143) or (144) were carried out following literature procedures[91, 92]. However multi-component mixtures were always obtained. The mixture contained the desired sulphone (143) or (144) and a series of piperazines (141) and (145) - (148) (Scheme 36).

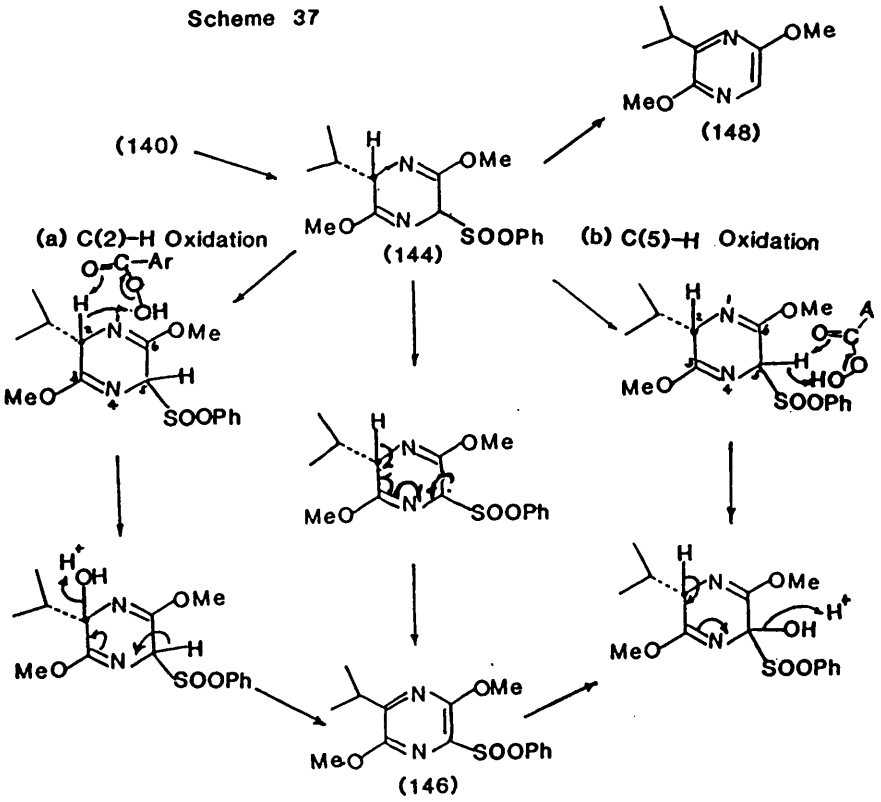
Scheme 36



Experimental results showed that when the temperature of reaction was lower and the concentration of oxidant was

lower, the desired oxidation to the sulphone was more favored. Otherwise, the side reactions appeared to be more competitive. Although the reasons for these side reactions remain unclear, a possible mechanism for generation of (145) and (146) is proposed as follows (Scheme 37):

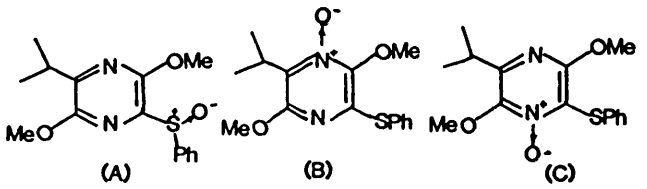
Scheme 37



The generation of (146) might go via either of two ways [C(2)-H oxidation or C(5)-H oxidation] although the C(5)-H oxidation seems more likely as it gives the more stable radical. The other aromatic products might also come from either C(5)-H oxidation-elimination or C(2)-H oxidation-

elimination. After manipulation of reaction conditions, a fairly good yield (65%) of desired compound (143) was obtained. Due to the facile aromatization of (143) and (144), it was necessary to use them soon after their preparation.

The structures of compounds obtained in this section, were confirmed by full spectroscopic data, some of which are listed in Table II . For example, a new compound was isolated which was spectrally closely related to (145) but was sixteen mass units greater suggesting (A), (B), or (C). structure (A) was excluded since no loss of 125 ($C_6H_5SO^+$) was observed. Only m/e 109 ($C_6H_5S^{+\cdot}$) was seen and (B) was preferred to (C) as the isopropyl methine proton was strongly deshielded.



As well as making the sulphone (129) via oxidation of the corresponding sulphide, attention was also given to its formation via bromination at the C-5 position (Scheme 38) followed by replacement of bromine with the phenylthio group.

Scheme 38

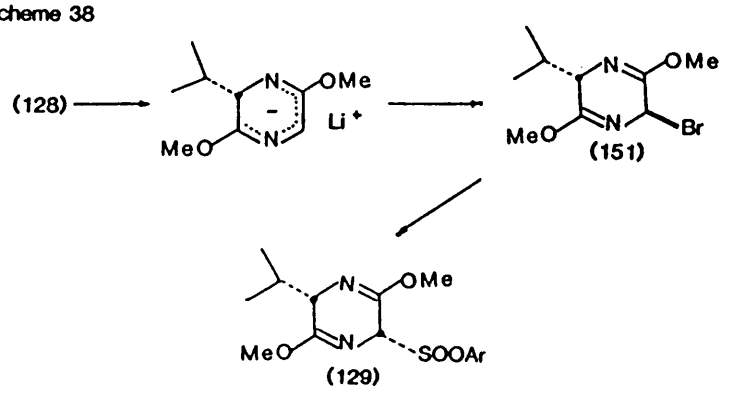


TABLE II

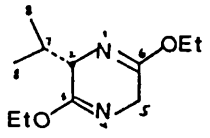
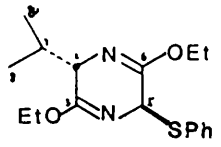
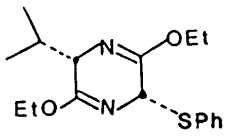
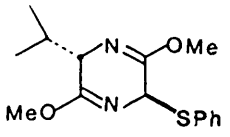
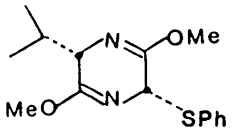
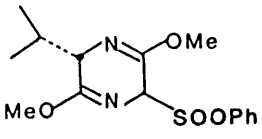
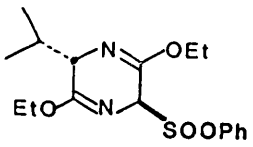
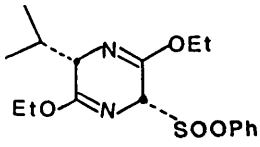
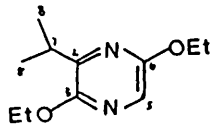
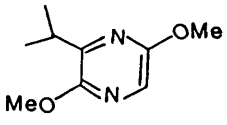
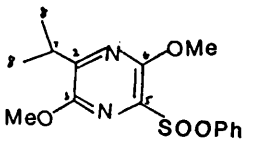
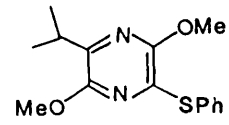
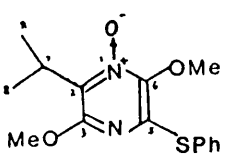
No of Compound and Structure	IR (cm^{-1})	MS	^{1}H-NMR (ppm)
	ν_{max}=1685(RO-C=N),1308 and 1025(=C-OR)	m/e=212(M^+, 55),184(100) 169(96),142 (58).	δ=3.96(3H,m,C-2,C-5),2.24(1H,m,C-7), 1.03(3H,d,J=7Hz,C-8_1),0.77(3H,d,J= 7Hz,C-8_2).
	ν_{max}=3060,1675, 1640,1305,740 (S-Ar).	m/e=321(M^++1 ,42),211(100),169(54), 141(12).	δ=7.22 7.45(5H,m,Ar-H),5.19(1H,d, J=3Hz,C-5),2.78(1H,dd,J=3Hz,7Hz, C-2),2.13(1H,m,C-7),0.89(3H,d,J= 7Hz,C-8_1),0.54(3H,d,J=7Hz,C-8_2)
			δ=7.24-7.36(5H,m,Ar-H ,5.29(1H,d,J= 2.5Hz,C-5),3.85(1H,dd,J=3.5Hz,5Hz, C-2),2.03(1H,m,C-7),1.04(3H,d,J=7Hz ,C-8_1),0.79(3H,d,J=7Hz,C-8_2).
	ν_{max}=3055(Ar-H), 1675,1650,1305, (RO-C=N),768,743 (S-Ar).	m/e=293(M^++1 ,42),183(100),141(50)	δ=7.13-7.46(5H,m,Ar-H),5.23(1H,d, J=3Hz,C-5),2.77(1H,dd,J=3Hz,4Hz, C-2),1.84 2.06(1H,m,C-7),0.90(3H, d,J=7Hz,C-8_1),0.52(3H,d,J=7Hz,C-8_2)
			δ=7.13-7.44(5H,m,Ar-H),5.32(1H,d,J= 4Hz,C-5),3.90(1H,dd,J=4Hz,7Hz,C-2), 1.96—2.15(1H,m,C-7),1.03(3H,d,J=7 Hz,C-8_1),0.72(3H,d,J=7Hz,C-8_2).
	ν_{max}=3060,1675, 1640,1455,1305, 1435,1420 and 1325(RSO_2Ar), 1260.	m/e=325(M^++1 ,42),183(100),141(43).	δ=7.56-8.16(5H,m,Ar-H),5.40(1H,d, J=4.5Hz,C-5),4.02(1H,dd,J=4.5Hz, J=6Hz,C-2),3.79(3H,s,MeO),3.68 3H,s,MeO),2.31(1H,m,C-7),1.06(3H, d,J=7Hz,C-8_1),0.62(3H,d,J=7Hz,C-8_2)

TABLE II (Cont.)

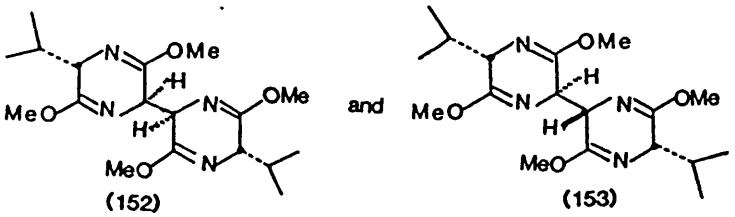
No of Compound and Structure	IR (cm^{-1})	MS	^1H-NMR (ppm)
	ν_{max}=3080,1670 and 1630(RO-C=N),1420 and 1325 (SO_2Ar),1305 and 1245(=C-OR)	m/e=353(M^++1, 42),211(100), 169(39)	δ=7.88(2H,m,o-Ar-H),7.55(2H,m,m-Ar-H),7.66(1H,m,p-Ar-H),5.28(1H,d,J=7Hz, C-5),3.84(1H,dd,J=3Hz,3Hz,C-2),2.30-245(1H,m,C-7),1.04(3H,d,J=7Hz,C-8_1), 0.61(3H,d,J=7Hz,C-8_2)
			δ=7.89(2H,m,o-Ar-H),7.67(1H,m,p-Ar-H),7.26(2H,m,m-Ar-H),5.30(1H,d,J=4.5 Hz,C-5),3.90(1H,dd,J=4Hz,6Hz,C-2), 2.20-2.31(1H,m,C-7),1.10(3H,d,J=7Hz, C-8_1),0.90(3H,d,J=7Hz,C-8_2)
	ν_{max}=3035,1330, 1260and 1030 (=C-OR).	m/e=210(M^+, 100),195(16),182(13),181(8),154(5)	δ=7.51(1H,s,C-5),3.30(1H,q,q,J=7 Hz,C-7),1.23(6H,d,J=7Hz,C-8_1 and C-8_2).
	ν_{max}=1555,1455, 1335(C=N in Ar) 1265,1035,1015, (=C-OR).	m/e=182(M^+, 25),167(32), 139(100),43 (26).	δ=7.65(1H,s,C-5),3.14(1H,qq,J=7Hz, C-7),1.24(6H,d,J=7Hz,C-8).
	ν_{max}=3060,1540, 1455,1335(C=N in Ar),1225(Ar-OR),1420 and 1320(SO_2Ar)	m/e=322(M^+, 2),141(37), 77(100),42 (14),28(98)	δ=8.05-8.12(2H,m,o-Ar-H),7.51-7.68 (3H,m,Ar-H),3.30(1H,qq,J=7Hz,C-7), 1.21(6H,d,J=7Hz,C-8)
	ν_{max}=3060,2850, 2960,1455(S-C), 1365,1135,1010.	m/e=290(M^+, 92),275(100) 260(25),109 (20),218(8).	δ=7.56(2H,m,o-Ar-H),7.35(2H,m,m-Ar-H),3.18(1H,qq,J=7Hz,C-7),1.19(6H,d, J=7Hz,C-8).
	ν_{max}=3050,1550, 1450,1365-1340, 1005(N-O),	m/e=306(M^+, 17),291(3), 290(5),275 (7),197(100) ,182(23),109 (12),167(20).	δ=7.80(2H,m,o-Ar-H),7.46(3H,m,Ar-H), 3.27(1H,qq,J=6.5Hz,C-7),1.20(6H,d,

Initially it was assumed that (151) could be generated by quenching the carbanion of (128) with a solution of Br_2 or NBS. Subsequently the bromide could be converted into the sulphone reagent (129) by a displacement reaction[82] or used directly in the cyclopropanation step instead of the sulphone reagent. Unfortunately, the bromination stage always resulted in a multi-component mixture. Neither reaction with Br_2 nor with NBS gave the desired compound (151). Two new compounds were isolated along with (148) and some starting material (128) from each reaction.

The mass spectrum of the first compound ($M^{+\cdot}$=366.2285, $C_{18}H_{30}N_2O_2^{+\cdot}$) indicated a dimeric structure derived from (128). The coupling constants $J_{2,5}=J_{2',5'}=2.5Hz$ showed C(5)-H and C(5′)-H are in a trans relationship with C(2)-H and C(2′)-H. The coincidence of chemical shifts i.e. 3.75ppm(6H,s,2 OMe), 3.54ppm(6H,s,2 OMe), (see experimental part) indicated the symmetry of this molecule. The chemical shifts were all consistent with those expected for structure (152), the trans dimerized product.

The second compound was confirmed as (153) under the following considerations: The molecular ion ($M^{+\cdot}$=366) indicated that the compound was dimeric ($C_{18}H_{30}N_4O_4$) and the coupling constants ($J_{2,5}$=4Hz, $J_{2',5'}$=6.5Hz) showed that C(2)-H is in the trans relationship with C(5)-H. Also, C(2′)-H is in the cis relationship with C(5′)-H. The four singlets (δ 3.67, 3.643, 3.637, 3.62 ppm) of the four methoxy groups and the

four doublets (δ 1.10, 1.05, 0.71, 0.69 ppm) of the four isopropyl methyl groups indicated the less symmetric character of the molecule. All these data were in accord with the structure (153) being a trans-cis-dimer of (128).

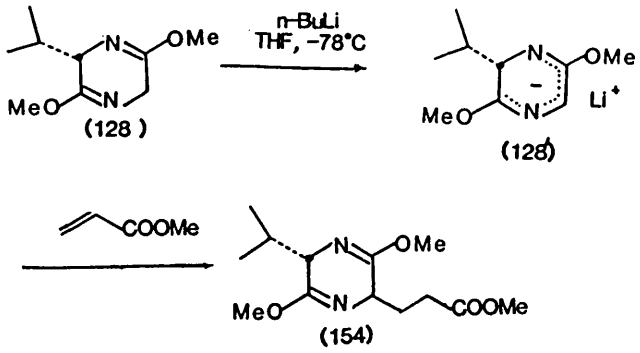


A possible explanation for the failure to isolate (151) could be that the desired compound might have been generated but quickly reacted with the carbanions to give dimer as well as aromatized compound .

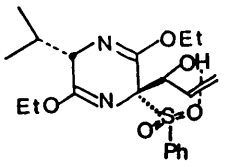
2-4 Attempted cyclopropanation via addition-elimination between the sulphone compound (142) and acrolein

Intermolecular nucleophilic addition to acrolein could go via either 1.2 or 1.4-addition. Initially a model reaction was done using the bislactim ether (128) and methyl acrylate (Scheme 39) following Schollkopf's procedure[83] and the desired compound (154) was obtained in 65% yield as hoped.

Scheme 39

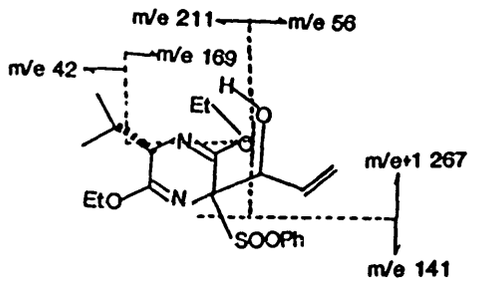


However when acrolein was used in place of methyl acrylate and 5-sulphonyl bislactim ether (129) was used in place of (128), 1,2-nucleophilic addition took place and only one compound (155) was obtained along with some uncharacterized polymers.



(155)

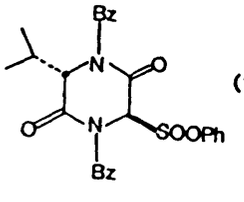
The IR spectrum of the product has a hydroxyl absorption at 3460cm^{-1}. The PMR spectrum is very similar to that of the starting sulphone except that (a) the signal 5.15-5.35ppm due to C(5)-H is no longer present and (b) five more protons [δ 5.01-5.40ppm(br, s, OH), 2.85 and 3.05ppm(d, J=10.5Hz, =CH-CH(OH))], corresponding to CH_2=CHCHOH- appear in the spectrum The mass spectrum was also in accord with structure (155).



In order to achieve Michael addition, lithium dialkylcuprate[94, 95] was used. Cuprous iodide was made by a standard method[96], and the reaction was carried out via generation of lithium dialkylcuprate, followed by addition of acrolein solution at -78^{0}C. Unfortunately again, a multi-component mixture resulted, and no desired 1.4-adduct or cyclopropane could be isolated, the only component characterized being the aromatized compound (146).

2-5 Attempted reaction with N,N′-dibenzyl 5-sulphonyl bis(Val-Gly-) lactam and methyl acrylate

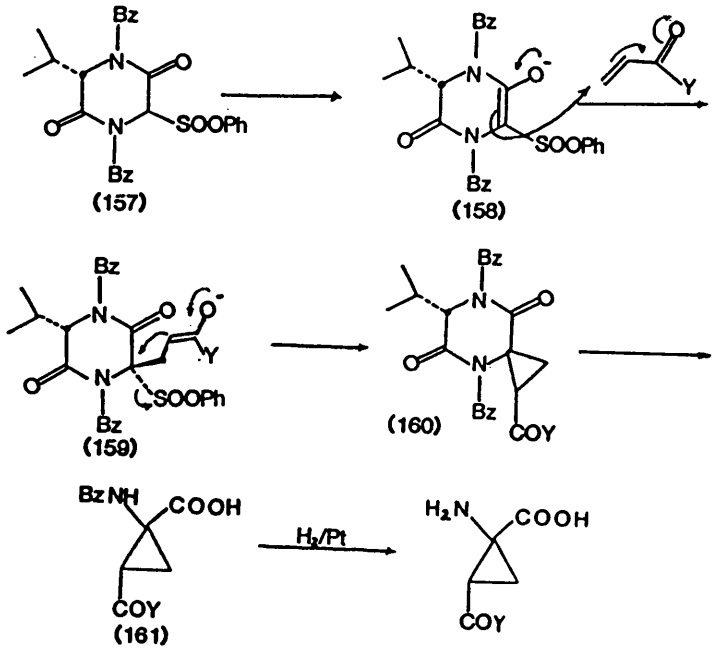
To avoid the serious aromatization problems which are associated with (129), a modified reagent (157) was proposed.



(157)

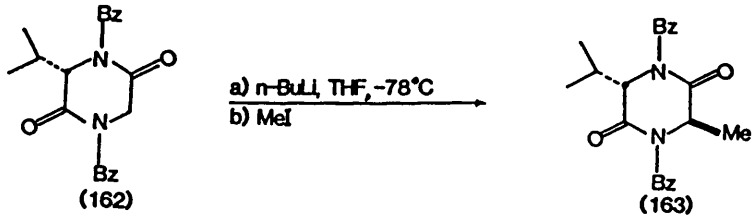
The advantage of this reagent (157) was its stability and the avoidance of aromatization. If it could also give high diastereoselectivity, it would be an ideal reagent for the syntheses of ACPAs (Scheme 40).

Scheme 40



Also, if cyclopropanation could be achieved, the benzyl group could be removed by hydrogenation[97]. To test the diastereoselectivity of this new reagent, the following reaction was performed (Scheme 41).

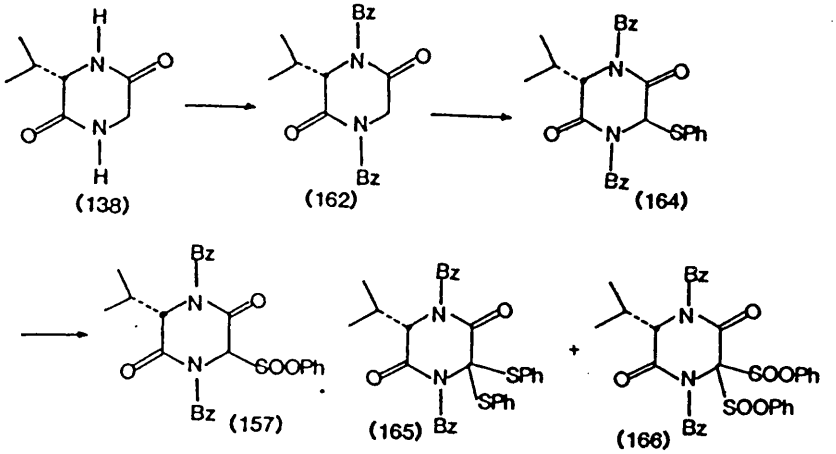
Scheme 41



Compound (162) was made in high yield (86%) by dibenzylation of the bislactam (138)[98]. As hoped, the methylation went with extremely high diastereoselectivity. The ratio of trans to cis isomer was about 20:1 as determined by ^{1}H-NMR.

The reagent (157) was prepared via a similar method to that used for (129)(Scheme 42).

Scheme 42



Reagent: a) NaH/DMF,BzCl ; b) n-BuLi/THF,-78°C,PhSSPh; c) mCPBA,-78°C , RT.

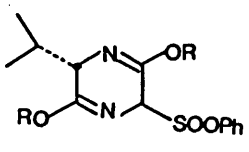
Initially, literature conditions[99a] were adopted for the N,N´-dibenzylation(NaH/THF). Unfortunately, an extremely poor yield of the desired product was obtained. Instead, when DMF was used as solvent, an excellent yield (86%) of (162) as a white solid was achieved. The sulphide (164) which contained a small amount of disubstituted compound (165), was also obtained in very high yield. Subsequent oxidation gave the sulphone (157) in 90% yield along with 3.5% of disulphone compound (166). All new compounds obtained in this section were confirmed by full spectroscopic analysis. Table II and Table III .

The addition-elimination reaction between (157) and methyl acrylate was examined with a range of bases(Et_3N, KOH, NaOMe, ^tBuOK, NaH) and solvents (ether, THF, DME, dioxane, H_2O) between -78°C to 70°C with sonication[99b]. Under none of these conditions was a cyclopropane formed. The failure of the reaction might be due to steric hindrance. The colour change produced when base was added suggests that the

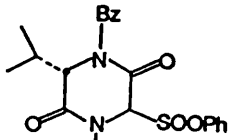
carbanion (158) was generated during the reaction.

2-6 Attempted cyclopropanation involving Schollkopf Reagent and methyl α-bromoacrylate :

The failure of both (129) and (157) to undergo the addition-elimination reaction was ascribed to the former being too unstable due to ready aromatization and the latter too stable due to steric hindrance.



(129)



(157)

An alternative route to ACPCs was considered. The reaction sequence proposed is outlined in Scheme 43 , where consecutive Michael addition, intramolecular carbanion exchange and elimination could lead to the desired compound (168).

Scheme 43

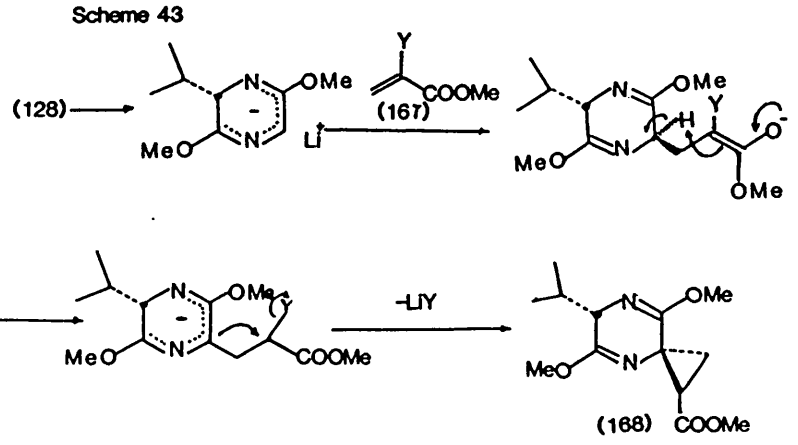


TABLE III

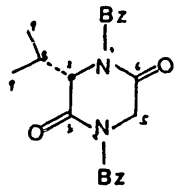
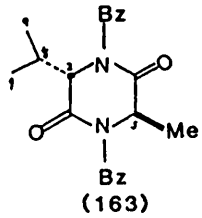
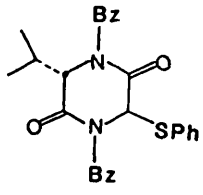
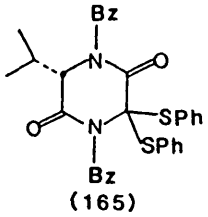
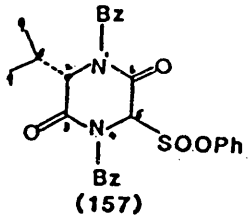
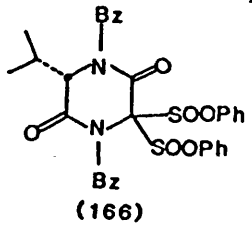
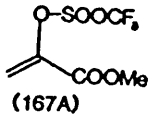
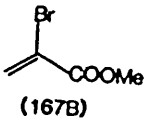
No of Compound and Structure	IR (cm^{-1})	MS	^1H-nmr (ppm)
 (162)	ν_{max}=3060,3025, 1650(C=O),1435, 1345,1325,1290, 1165,725,700	m/e=336(M^+, 18),293(19), 92(8),91(100	δ=7.18-7.37(10H,m,Ar-H),5.37(1H, d,J_{BA}=14.5Hz,C-7_A),4.81(1H,d,J_{AB} =14.5Hz,C-10_B),4.29(1H,d,J_{BA}= 14.5Hz,C-10_B),3.97(1H,d,J=17.5Hz C-5_A),3.91(1H,d,J_{BA}=17.5Hz,C-5_B) ,3.77(1H,d,$J_{2,8}$=6.5Hz,C-2),2.21 (1H,m,C-8),1.09(3H,d,J=7Hz,C-9_1) ,0.92(3H,d,J=7Hz,C-9_2)
 (163)	ν_{max}=3060,3030, 1645(C=O),1435, 1355,1290,1170, 730,700	m/e=350(M^+, 18),307(21) ,279(6),91 (100)	δ=7.19-7.39(10H,m,Ar-H),5.45(1H, d,J_{AB}=15Hz,C-7_A),5.35(1H,d,J=15Hz C-10_A),4.16(1H,d,J=15Hz,C-7_B), 4.06(1H,q,J=7Hz,C-5),3.94(1H,d, J_{BA}=15Hz,C-10_B),3.81(1H,d,J=5Hz, C-2),2.31(1H,m,J=5Hz,7Hz,C-8), 1.59(3H,d,J=7Hz,C-11),1.13(3H,d, J=7Hz,C-9_1),0.95(3H,d,J=7Hz,C-9_2)
 (164)	ν_{max}=3060,3030, 1655,1575,1435, 1250,1165,735, 690	m/e=445(M^++ 1,12),377(3) 335(65),141 (52),109(73),91(100)	δ=7.67-7.68(5H,m,SAr-H),7.10-7.3 -4(10H,m,Ar-H),5.41(1H,d,J_{AB}=15 Hz,C-7_A),5.39(1H,d,J=15Hz,C-10_A) 4.96(1H,s,C-5),3.98(1H,d,J=15Hz, C-7_B),3.92(1H,d,J=15Hz,C-10_B), 3.71(1H,d,J=7.5Hz,C-2),2.31(1H,m ,J=7.5Hz,7Hz,C-8),1.19(3H,d,J=7 Hz,C-9_1),1.13 (3H,d,J=7Hz,C-9_2)
 (165)	ν_{max}=1655(C=O), 1575,1435,1250	m/e=553(?), 445(12),377 (3),335(65), 141(52),109 (73),91(100)	δ=7.70-6.82(20H,m,Ar-H),5.62(1H ,d,J_{BA}=14.5Hz,C-7_A),4.60(2H,s, C-10),4.45(1H,d,J_{BA}=14.5Hz,C-7_B),3.76(1H,d,$J_{2,8}$=5Hz,C-2),2.19 (1H,m,$J_{8,2}$=5Hz,$J_{8,9}$=7Hz,C-8), 0.95(3H,d,J=7Hz,C-9_1),0.64(3H,d ,J=7Hz,C-9_2)

TABLE III (Cont.)

No of Compound and Structure	IR (cm^{-1})	MS	^{1}N-nmr (ppm)
 (157)	ν_{max}=1665,1575, 1440,1420,1145 ($ArSO_2R$)	m/e=477(M^++1, 18),335(100), 143(13),91(68)	δ=7.25-7.98(5H,m,Ar-H),7.05-7.30(10H,m,Ar-H),5.72(1H,d,J=15 Hz,C-7_A),5.44(1H,d,J=15Hz,C-10_A) 5.08(1H,s,C-5),4.13(1H,d,J=15Hz, C-7_B),3.93(1H,d,J=15Hz,C-10_B), 3.67(1H,d,J=9.5Hz,C-2),2.65(1H,m ,J=9.5Hz,7Hz,C-8),1.25(3H,d,J=7 Hz,C-9_1),1.22(3H,d,J=7Hz,C-9_2)
 (166)	ν_{max}=1670,1570, 1435(d),1385-1360,1336,1195	m/e=616(?), 507(6),335 (45),336(24),337(30), 293(7),91 (100)	δ=7.41-8.10(10H,m,SO_2Ph),7.23-7.37(10H,m,Ar-H),5.41(1H,d,J=15 Hz,C-7_A),4.97(2H,s,C-10),4.07(1H ,d,J_{BA}=15Hz,C-7_B),4.00(1H,d,$J_{2,8}$ =4Hz,C-2),2.24(1H,m,$J_{8,2}$=4Hz, $J_{8,9}$=7Hz,C-8),0.96(3H,d,J=7Hz, C-9_1),0.62(3H,d,J=7Hz,C-9_2)

The idea combines a well established intramolecular cyclopropanation method[100,101] with Schollkopf methodology[53]. In order to achieve this purpose , compounds (167A) and (167B) were chosen as reagents.

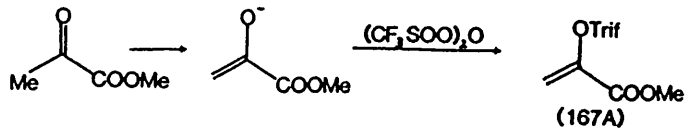

(167A)


(167B)

Since the triflate is assumed to be the best leaving group[102], and is about 500 times more reactive than tosylate[103], the synthesis of (167A) was made the first priority. Although not previously prepared, methods for its

synthesis, based on those of other vinyl triflates [104] could be envisaged. The first attempt was made by generating the carbanion of methyl pyruvate with n-BuLi before treatment with triflic anhydride $(CF_3SO_2)_2O$ and the second by reaction of the ester with the triflic andydride and pyridine[104](Scheme 44):

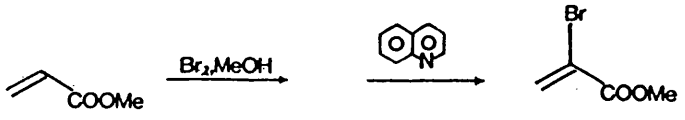
Scheme 44



(167A)

A quickly taken PMR spectrum of the crude reaction product shown in each cases, that (167A) had been formed (data see experimental part), but it proved too unstable to purify and gave no desired reaction products. As the triflate reagent was too unstable to handle, α-bromo acrylate was proposed as an alternative reagent and prepared according to (Scheme 45)[106] :

Scheme 45

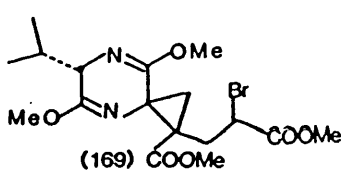


(167B)

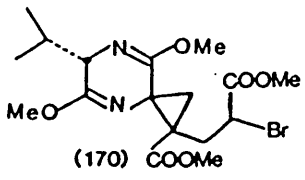
The first step was carried out smoothly under 40^0C. and a nearly quantitive yield was obtained. The selective debromination was performed at 100^0C. After distillation of the crude product, a good overall yield (87%) of (167B) was achieved.

The addition-elimination reactions were examined under various conditions(Table IV). Initially, n-BuLi was used as base in THF solution with temperature, concentration and reaction time being varied. After work up, no methyl bromoacrylate could ever be detected, and a multi-component mixture containing starting material (128) was always generated. The only identifiable products were two isomers. The ^{1}H-NMR spectrum showed two methyl esters in each isomer and the mass spectrum showed M^+433(100%) along with M^++2 435(98%) indicating that there was only one bromine atom in each molecule, consistent with possible pairs of diastereoisomers such as (169), (170) and (171), (172):

Scheme 46

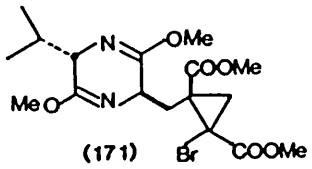


(169)

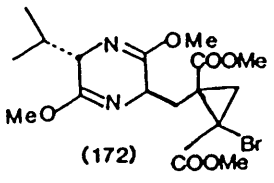


(170)

Scheme 47



(171)



(172)

The structures of (169) and (170) were excluded since C_5-H gives rise to a doublet of doublets (appearing as a triplet) due to a vicinal coupling of the same magnitude as the $J_{5,2}$ of C(5)-H to the C(2)-H, and not as the doublet required for compounds (171), (172). Since the chemical shift of the isopropyl group of two compounds (171), (172) are similar, and the coupling constants for C_5-H and C_2-H ($J_{2.5}$=4.5Hz) are very similar to the trans 2,5-dialkyl

pyrazines prepared by Schollkopf[37a], then the new substitutent group connected at C-2 should be trans to the isopropyl group.

Possible structures for these two isomers are based on ^{1}H-NMR data (Table V).

Table V

The chemical shifts (ppm) and coupling constants (Hz) for compounds (171) and (172)

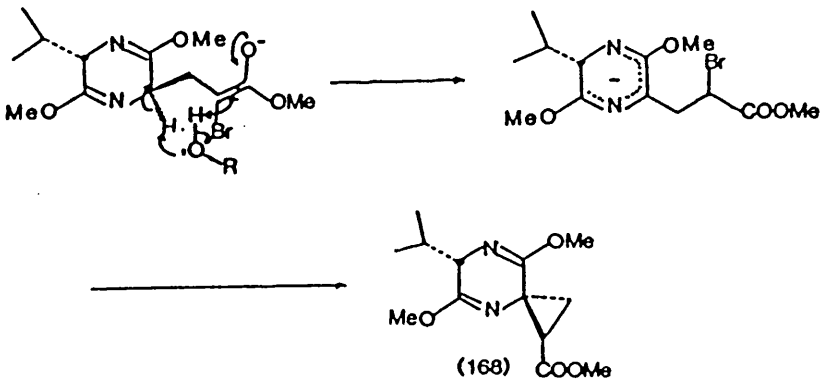
C-X-H	Isomer 1	Isomer 2
C-2-H	4.23(1H,ddd, J_{XA}=8, J_{XB}=4.5, $J_{2,5}$=4.5)	4.07(1H,ddd, J_{XA}=6, J_{XB}=9,$J_{2,5}$=4.5)
C-5-H	3.97(1H,dd, $J_{5,2}$4.5, $J_{5,13}$=3)	3.93(1H,dd, $J_{5,2}$=4.5, $J_{5,13}$=3)
C-7_A-H	1.98(1H,dd, J_{AX}=8, J_{AB}=14)	2.25(1H,dd, J_{AX}=6, J_{AB}=14)
C-7_B-H	3.00(1H,dd, J_{BX}=4.5, J_{BA}=14)	2.68(1H,dd, J_{BX}=9, J_{BA}=14)
C-10_A-H	1.49(1H,d, J_{AB}=7)	1.41(1H,d, J_{AB}=7)
C-10_B-H	2.43(1H,d, J_{BA}=7)	2.50(1H,d, J_{BA}=7)
C-13-H	2.24(1H,m, $J_{13,5}$=3, $J_{13,14}$=7)	2.24(1H,m, $J_{13,5}$=3, $J_{13,14}$=7)
C-14_1-H	1.04(3H,d, $J_{14,13}$=7)	1.04(3H,d, $J_{14,13}$=7)
C-14_2-H	0.69(3H,d, $J_{14,13}$=7)	0.69(3H,d, $J_{14,13}$=7)

Since these cyclopropane analogues were not our target compounds, no particular effort was given to further prove these structure or to improve the yield.

Much effort was given to the manipulation of reaction conditions in order to stop the second Michael addition occuring [(Table IV), page 73] involving variations of (a) base (n-BuLi, Et_3N,KOH); (b) temperature (from -78°C to RT); and (c) reaction time. Only double Michael addition along with the recovery of starting material was observed.

To get around this problem, modified conditions were employed based on the idea of forcing the reaction to go by changing from the sterically unfavoured four-membered ring to the sterically more favoured six-membered ring transition state. It was assumed that some protic solvent might help the proton transfer reaction (Scheme 48).

Scheme 48



Two variations of reaction conditions have been explored, so far, based on this idea:

(i) ^tBuOK / THF, -78°C to RT. 48 hours, with sonication;

(ii) ^tBuOK / DMF, 0°C to RT, 40 hours .

TABLE IV

No.		1	2	3	4	5	6	7	8	10	11
Solvent		THF	THF	THF	THF	THF	THF	DCM + H_2O	THF	THF	DMF + ^tBuOH
Generation of carbanion	Base (equiv.)	n-BuLi (1.1)	n-BuLi (1.1)	n-BuLi (1.1)	n-BuLi (1.1)	n-BuLi (1.1)	Et_3N (1.1)	KOH (5%)	n-BuLi (1.1)	n-BuLi (1.1)	n-BuLi (1.1)
	Time(min)	15	15	15	15	15	15	15	15	20	
	Temp.	-78°C	-78°C	-78°C	-78°C	-78°C	RT	RT	-78°C	-78°C	
Addition of (165)	equiv.	1	1	1	1	1	1	1	1	1	1
	Temp.	-78°C	-78°C	-78°C	0°C	RT	RT	RT	-35 to -40°C	20°C	0°C
	Time(h)	0.5	0.5	0.5	1	1	1	1	1	1	1
Reaction method	Temp.	-78°	-78°C	-78°C	0°C	RT	RT	RT	-40°C	-20°C	0°C to RT
	Time(h)	1	2.5	5	1	2	48	96	1/12	0.25	5
	a'. Method				g.	g.	i.	j.			k.
Quenching	Reagent	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$	NH_4Cl $+H_2O$
	Temp	-78°C	-78°C	-78°C	0°C	RT.	RT	RT	40°C	30°C	RT
Results		a,b,c	a	b,d	b,c	e	e	e	e	e	e

a'. Additional method.

a. Most staring material recovered.

b. Multi-component mixture obtained.

c. No desired product was detected from GC-MS.

d. Small amount of (171) and (172) was isolated.

e. No reaction.

f. additional method.

g. Very dilute solution.

i. Speeded up by ultrasonic bath.

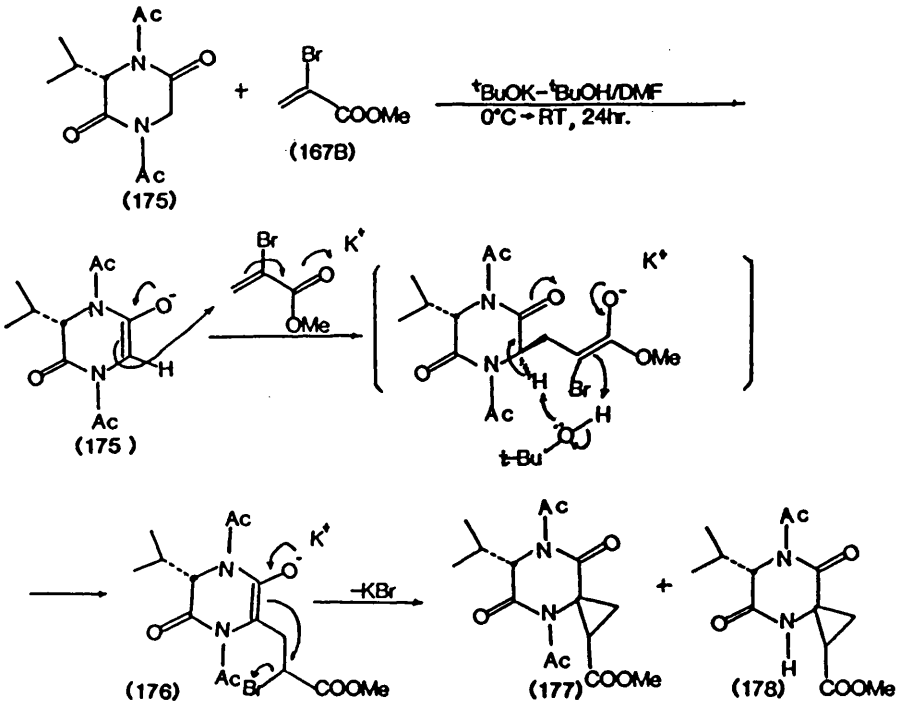
j. Using BTEAC as phase-transfer catalyst.

k. The reaction solution was fairly concentrated.

Although in the first case over 95% and in the second nearly 80% bislactim ether were recovered from these reactions, but, the data ($M^{+\cdot}$=268(1%)) obtained from GC-MS suggested that this $M^{+\cdot}$ might relate with the molecular weight of the desired spiro-cyclopropane derivatives (168).

Due to the extremely poor conversion, no futher effort was made on Schollkopf´ reagent, instead, the N,N-diacetyl diketopiperazine (175) was prepared and its reaction with (167B) was investigated (Scheme 49):

Scheme 49

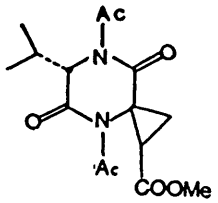


After purification of the crude product by column chromatography and allowing for a 35% recovery of starting material, the conversion of (175) to (177) and (178) was accomplished in 24% yield in a ratio of 1:4. This could

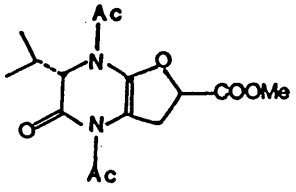
undoubtedly be improved but lack of time prevented optimization of the procedure.

The structures of (177) and (178) were confirmed as follows: The IR spectrum of the first compound had a strong absorption at 1735cm^{-1} (CO_2Me), and the mass spectrum ($M^{+\cdot}$= 324.1324) was consistent with one of two possible structures (177) and (179) (Scheme 50)

Scheme 50



(177)



(179)

Structure (179) is excluded by the ^{1}H-NMR spectrum, since 3.45ppm (1H, d,d, J_{XA}=9Hz, J_{XB}=6Hz, C_X-H) is too high to be considered for the C-14-H of (179). Other evidence for structure (177) is the fact that the N-4-Ac group is strongly shielded [δ=1.93(3H, s, N-Ac)ppm] which suggests that there is a carboxy group adjacent N-4-Ac and this is also in accord with the structure (177).

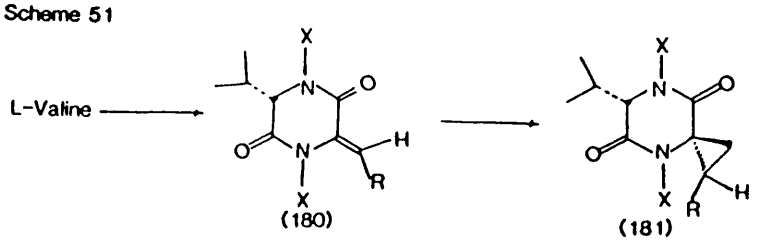
The compound (178) was confirmed by comparision with the data for (177). This compound has very similar spectral data, but (a) it has a strong absorption at 3440cm^{-1}(N-H, st.); (b) the molecular ion is 42 units less than that for (177)[$M^{+\cdot}$of (178)=282]; (c) only one N-Ac group (δ=2.59ppm) can be found in its PMR spectrum. All other data are in accord with the structure (178).

Chapter 3 : The asymmetric syntheses of ACPCs via α,β-dehydroamino acid derivatives

3-1 Introduction

Along with the addition-elimination approach to induce ACPCs enantioselectively, another approach was explored, via the addition of carbene or carbenoids to α,β-dehydroaminoacid derivatives. The initial idea was based on the discovery of Izumiya[109], who hydrogenated cyclo(α,β-dehydro-Ala-L-Leu) and observed unexpectedly high asymmetric induction, affording pure cyclo-(α,β-dehydro-L-Ala-L-Leu). Assuming that the difference in approach to the two faces of cyclic dipeptides such as (180) containing α,β-dehydroaminoacids might induce high asymmetric cyclopropanation, a novel strategy for chiral syntheses of cyclopropanes derived from amino acids was proposed as follows (Scheme 51).

Scheme 51



Presumably, the carbon-carbon double bond faces in (180) are sterically differentiated towards reagent approach due to the isopropyl group. If so, then a route to chiral ACPC's is apparent.

3-2 Synthesis of N,N-diacetyl-2-alkylidene-5-isopropyl-3,4-piperazinediones (180)

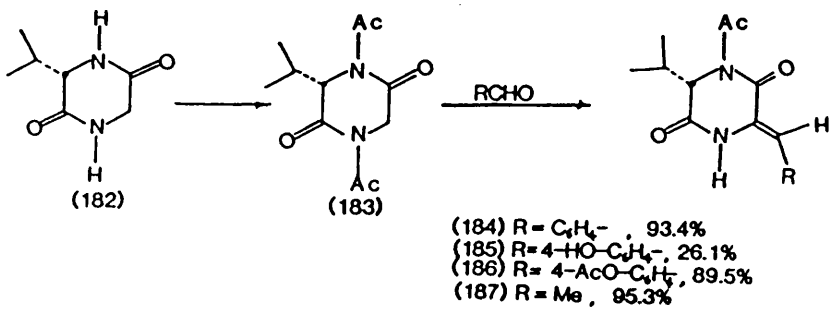
There are two routes to the key reagent (180) :

(a) by synthesis of the dehydroamino acid first[110] following by its incorporation into a piperazine ring.

(b) by synthesis via an aldol condensation between a diketo piperazine and aldehyde.

As route (b) is more general and the method has been well developed since the 1920's[111], the aldol condensation was the route of choice(Scheme 52).

Scheme 52



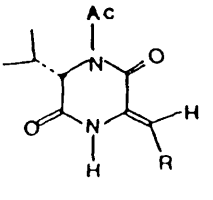
(184) R = C_6H_5- , 93.4%
(185) R= 4-HO-C_6H_4-, 26.1%
(186) R= 4-AcO-C_6H_4-, 89.5%
(187) R = Me , 95.3%

Precursor (182) was prepared from L-valine and glycine via the

method described before. Treatment of (182) with Ac_2O at 130^{o}-$135^{o}C$ for 12 hours gave (183) in over 90% yield. Surprisingly the results of chiral lanthanide shift ^{1}H-NMR studies of (183) showed that no racemization of the L-Val residue had occurred in spite of the quite drastic conditions. This is in agreement with a similar observation on a related derivative made by Izumiya et al.[109b].

Since Gallina[111] has reported that cyclo(NAc-Gly-NAc-Gly) reacts easily with aldehydes in the presence of t-BuOK, their procedure was adapted for our reaction. Surprisingly, only one geometrical isomer was generated in excellent yield in each case for benzaldehyde (Scheme 52) or p-acetoxybenzaldehyde. Hówever in the case of acetaldehyde, two isomers [(187a) and (187b)] were generated, the ratio being greater than 19:2 as determined by ^{1}H-NMR.

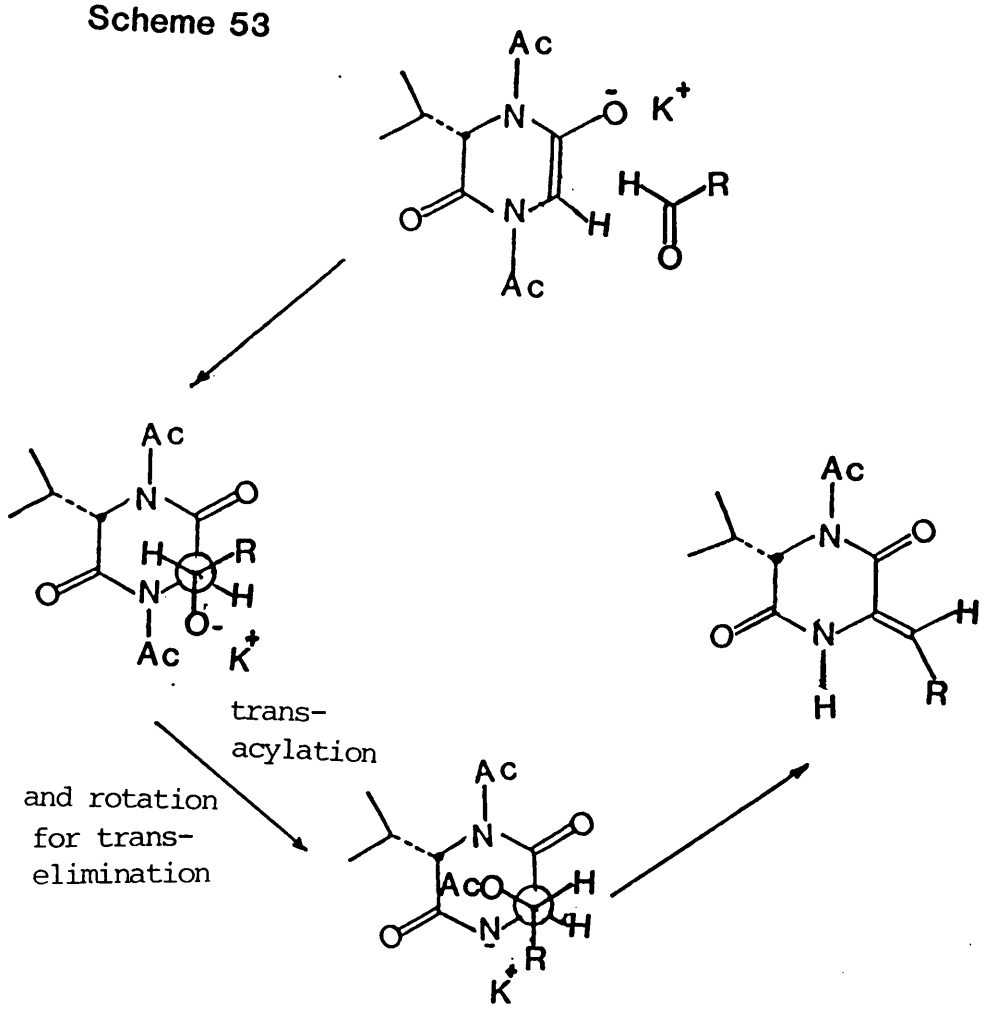
In order to confirm the relative stereochemistry of the main products, NOE measurements have been carried out on these compounds. As these showed no effect on the vinyl hydrogen when N-H was irradiated, but in contrast, enhancement of the methyl signal (when R=Me) and the o-phenyl-protons (when R=phenyl) were observed. The structure of the major isomers



were therefore confirmed as the thermodynamically more stable Z-isomers.

The following mechanism was proposed to explain the observation (Scheme 53):

Scheme 53

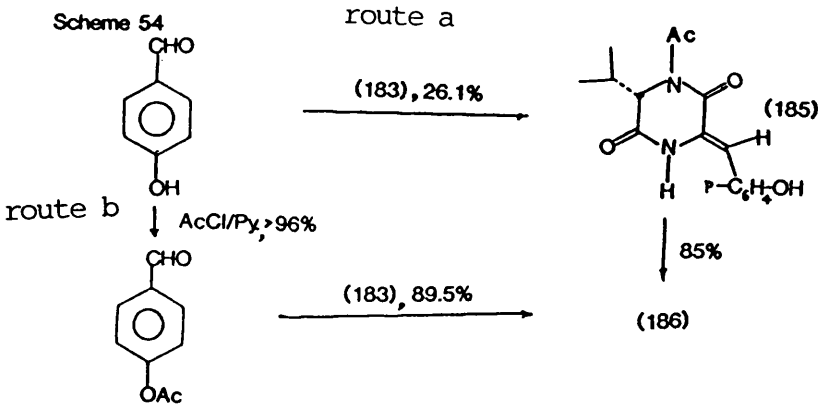


As for the stereochemical outcome of the reaction, results of chiral lanthanide shift studies showed that excellent chiral integrity was maintained during the condensation reaction. The aldol condensation between (183) and benzaldehyde was carried out, initially, in the presence of 1.1 equivalents of ^{t}BuOK,

when nearly 80%ee in the aldol condensation product was obtained. It was assumed that the partial racemisation was caused by excess base and consequently the reaction was repeated using one equivalent of ^{t}BuOK. Gratifyingly, the preparation using such conditions gave greater than 95% ee as assessed using chiral lanthanide shift reagent. (No racemized product could be detected from the chiral lanthanide NMR study of these products).

The compound (186), was prepared in two ways as follows in (Scheme 54)

Scheme 54



At first, 4-hydroxybenzaldehyde was used directly for the condensation. Unfortunately, a very poor yield of (185) was achieved. The product was acetylated (1.1 equiv. AcCl/Py in toluene) in 85% yield. Owing to the poor yield via route (a), route (b) was followed as an alternative. The first step, N-acetylation, was carried out in the presence of acetyl chloride and pyridine in a solution of ether and an excellent yield (96%) was achieved. The second step, aldol condensation,

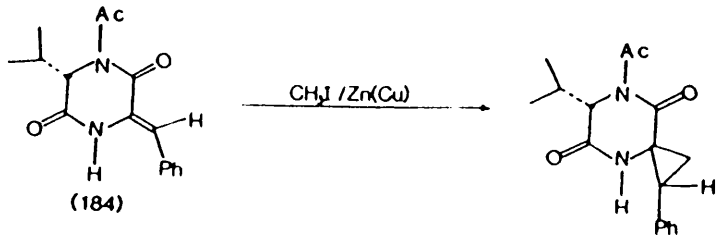
was performed under normal conditions. Again, one single isomer was achieved in very high yield (89.5%) without detectable racemization.

3-3 The cyclopropane construction:

A review of the literature reveals that there are three major methods which can be employed, (a) carbene addition to an olefinic bond where the carbene is obtained by copper catalyzed decomposition of diazo compounds[112]; (b) Simmons-Smith reaction to generate a carbene by reductive elimination of iodine from gem-diiodides[113]; and (c) the addition of sulfonium ylides to α,β-unsaturated carbonyl compounds[114].

Due to the extremely high stereoselectivity which has been found in Simmons-Smith reaction[115], one of our experiments was performed accordingly (Scheme 55).

Scheme 55



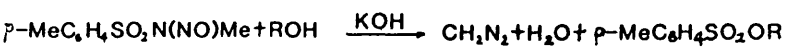
The Zn(Cu) couple was freshly made by a literature method[116], and the reaction was carried out by reference to the method described by Simmons,Mash et al. [117 to 119]. Unfortunately no product could be identified, most of the starting material being recovered from the reaction.

The possible reason for failure to react might be the specificity of this reaction for non-activated double bonds. No evidence for its application on activated double bonds could be found in the chemical literature.

The addition of sulfonium ylides was considered as they are specific for activated double bonds and steric hindrance is of little importance in these reaction because the C-S bond is long[120].

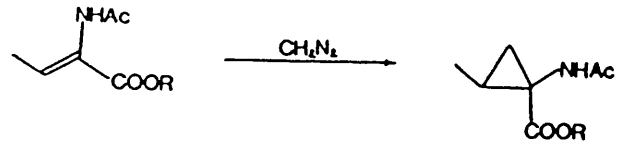
When one equivalent of a sulfonium ylide was used following Trost's procedure[121], a multi-component mixture was generated along with some unreacted starting material. Finally, effort was directed towards the diazomethane reaction, the reagent being generated from diazald (N-nitroso-N-methyl tosylamide) and KOH[122] (Scheme 56).

Scheme 56

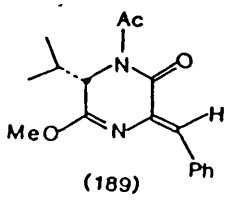


and the reaction carried out over a period of 30hr.. Although it is known that diazomethane can react with N-H, it was hoped that it would react with the double bond first as shown by Stammer[31], who successfully obtained a cyclopropane without the N-methylation product(Scheme 57).

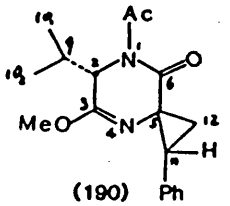
Scheme 57



In our case, two isomers were isolated in modest yield when slightly more than one equivalent of diazomethane was used.



(189)

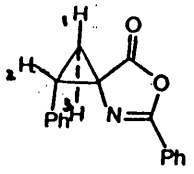


(190)

The spectroscopic data for the first compound (Rf=0.65, DCM) are quite similar to those for the starting (184) except: (a) 14 units more ($M^{+\cdot}$=300) in the mass spectrum; (b) no N-H absorption (ν_{max} 3210cm^{-1}) in its IR spectrum and (c) one MeO(N=C-OMe) more (δ 3.97ppm) in its ^{1}H-NMR, all of which are in accord with the structure (189).

The structure of the second compound (Rf=0.60, DCM) was elucidated spectroscopically.

It had similar spectral data to (189), but was 14 mass units higher ($M^{+\cdot}$=314) in its mass spectrum. No conjugated vinylic proton (=C-H) was observed in the ^{1}H-NMR spectrum, instead, an ABX system was observed [δ 2.98(1H, dd, J_{XA}=8.5 and J_{XB}=10Hz, C-11-H), 2.38(1H, dd, J_{BA}=-5.5 and J_{BX}=10Hz, C-12$_B$-H), 1.89(1H, dd, J_{AB}=-5.5 and J_{AX}=8.5Hz, C-12$_A$-H)]. The chemical shifts and coupling constants were similar to those for a phenyl-substituted spirocyclopropane derivative (191)[22], suggesting that the compound is (190). The higher resolution mass measurement ($M^{+\cdot}$=314.1621) was also in accord with structure (190).



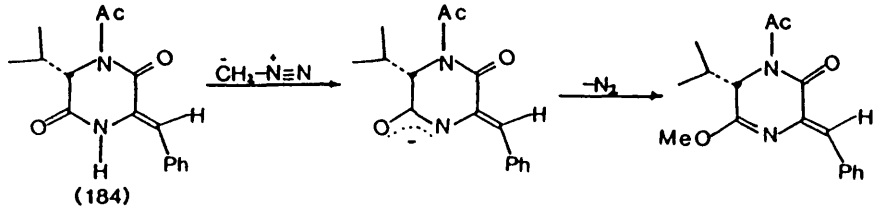
(191)

Z-isomer:

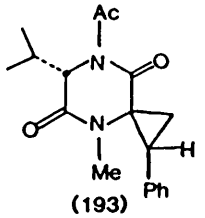
v(ppm)	J(Hz)
v_1=2.38	$J_{1,2}$=-5.5
v_2=2.24	$J_{1,3}$=8.7
v_3=3.20	$J_{2,3}$=9.7

The following mechanism is proposed (Scheme 58)

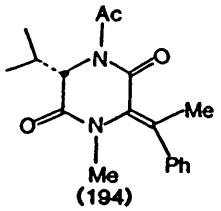
Scheme 58



Influenced by the phenyl group as well as the double bond, the enol form might be slightly more favored than in the ordinary amides, and the diazomethane might thus react fast with the hydroxyl group than with the carbon-carbon double bond. The cyclopropane product would be generated by the excess of diazomethane. In consequence, a larger excess of diazomethane (more than 2 equivalents) was employed in further reactions. No product (189) was isolated. Both the desired cyclopropane (190)(33%) and the N-methylated cyclopropane (193)(19%), were isolated together with side product (194)(27%).



(193)



(194)

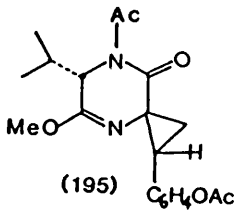
The structure of the compound (193) was confirmed by comparision with (190). Both had the same molecular weight ($M^{+\cdot}$=314), very similar IR and ^{1}H-NMR spectral data except that (193) showed at δ 2.85ppm(3H, s, N-Me) instead of an OMe absorption δ 3.50ppm(O-Me).

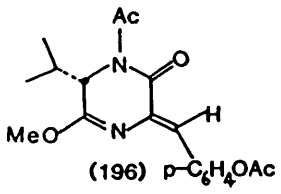
Structure (194) was assigned by comparison with the starting material (184). Both of them have very similar IR spectra apart from the lack of NH absorption in (194)(ν_{max} 3210cm^{-1}) It was 28 mass units more than (184). In the NMR spectrum, no N-H and conjugated vinyl proton was observed.

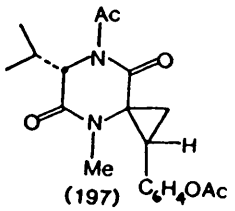
Instead, one more N-Me(δ 2.63ppm) and one more Me(=C-Me) (δ 2.47) appeared. All data were in agreement with structure (194).

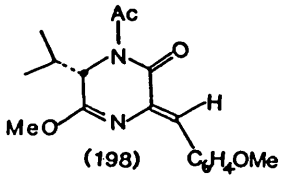
It seems that competitive N-methylation is more favored when the concentration of diazomethane increases. These conditions were applied to compound (186) and a mixture of (195)- (198) were obtained.

Scheme 59



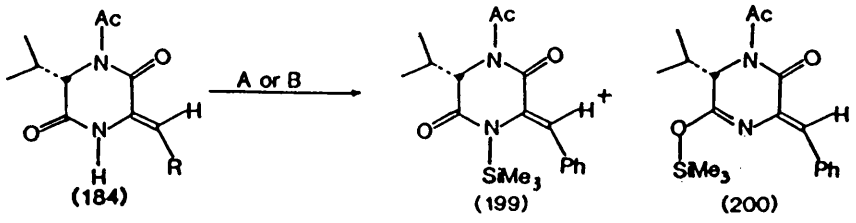






In order to avoid the unwanted N-methylated product, efforts were made to protect NH before cyclopropanation. The TMS group was initially chosen as it has the advantages of easy introduction and removal (Scheme 60).

Scheme 60



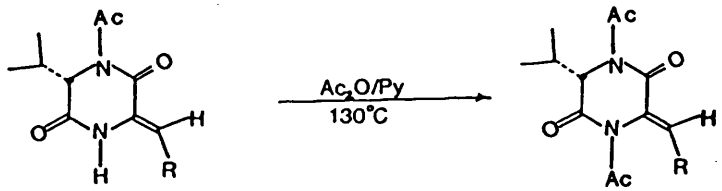
Method A: NaH/Me_3SiCl, ether, 0^0C to RT, 2 hours.

Method B: $Me_3Si\text{-}N^+Et_3\ Cl^-$, 0^0C to RT, 16 hours.

Although both methods A and B were explored, no satisfactory results were obtained from either of them. When the reactions were worked up by completely dry methods , a mixture of three products, (184), (199) and (200), was obtained, but because (199) and (200) are so labile, no pure (199) and (200) could be isolated, decomposition taking place on silica or alumina column packings. Both (199) and (200) could be detected from the ^{1}H-NMR spectrum of the crude product.

Due to the failure to obtain the desired silyl compound, the acetyl group was chosen as an alternative protective group. (Scheme 61):

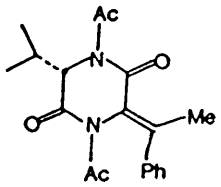
Scheme 61



(184) R = Ph-
(186) R = $AcOC_6H_4$-

(201) R = Ph-
(202) R = $AcOC_6H_4$-

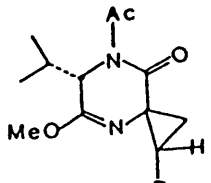
The acetylation reactions were carried out as described before, and (201) and (202) were obtained in yields of 84% and 75% respectively. Their cyclopropanation reactions were attempted as described before (diazomethane, ether solution, RT, 50 hours) and again, neither of the desired cyclopropanes, were isolated but the methylated compound (203) was the only product obtained, in 27% yield.



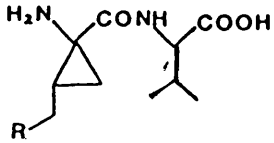
(203)

The structures of all new compounds obtained in this section were confirmed by spectroscopic data and correlation with data from our previous compounds. The major data are listed in (Table VI).

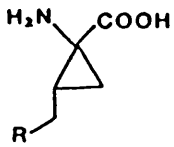
In conclusion, a method has been established for the synthesis of spirocyclopropyl diketopiperazines of structure (204) and it remains now to establish methodology for hydrolyzing them into dipeptides (205) and cyclopropyl amino acids (206). These studies are the focus of a further postgraduate programme.



(204)



(205)



(206)

TABLE VI

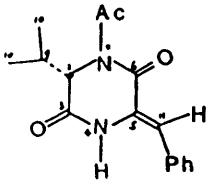
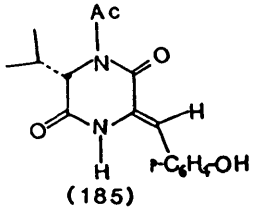
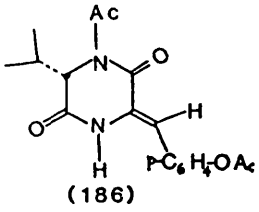
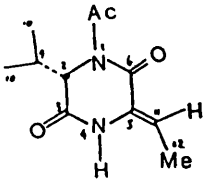
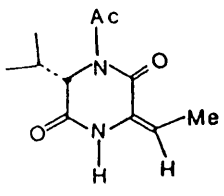
No of Compound and Structure	IR (cm^{-1})	MS	^1H-NMR (ppm)
 (184)	ν_{max}=3210(NH), 1690(C=O), 1620 1365, 1225, 1200	m/e=286(M^+,75), 244(15) 202 (100) 173 (37)	δ=8.33(1H,s,NH), 7.35-7.45 (5H,m,Ar-H),4.97(1H,d,J=7Hz, C-2),2.59(3H,s,N-Ac),2.12(1H, m,J=7Hz,C-9),1.06(3H,d,J=7Hz, C-10_1),1.05(3H,d,J=7Hz,C-10_2) 7.15 (1H,S, C-11).
 (185)	ν_{max}=3370-3150 (OH,NH), 1760, 1685,1620(C=O) 1595(arC-C), 1365,1225,1195 (Ar-O)	m/e=302(M^+,30)	δ=8.65(1H,br,s,NH),7.60(1H, br,s,OH),7.50(2H,d,J=9Hz , o-Ar-H),7.25(2H,d,J=9Hz,m-Ar-H) 7.15(1H,s,C-11),5.05(1H,d,J=7Hz, C-2),2.65(3H,s,N-Ac),2.10(1H,m, C-9),1.25(3H,d,J=7Hz,C-10_1),1.07 (3H,d,J=7Hz,C-10_2)
 (186)	ν_{max}=3250(NH), 1760,1695 and 1620(C=O), 1365,1225,1195 1165	m/e=344(M^+,32) 302(99),260(30) 218(52),217(68) 189(23),43(100)	δ=8.34(1H,br,s,NH),7.47(2H,d, o-Ar-H),7.18(2H,d,J=9Hz,m-Ar-H), 7.12(1H,s,C-11),4.97(1H,d,J=7Hz, C-2),2.59(3H,s,N-Ac),2.32(3H,s, O-Ac),2.13(1H,m,C-9),1.05(3H,d, J=7Hz,C-10_1),1.04(3H,d,J=7Hz, C-10_2)
 (187) (Z-isomer)	ν_{max}=3200(NH), 1695,1675,1640 (C=O),1365 , 1230,1165	m/e=224(M^+,18) 182(22),140 (49),139(30) 111(16),43 (100)	δ=9.35(1H,br,s,NH),6.41(1H,q, J=7Hz,C-11),4.92(1H,dd,$J_{2,9}$=7.5 Hz,$J_{2,NH}$=1.5Hz,C-2),2.53(3H,s,N-Ac),2.05(1H,m,$J_{9,2}$=7.5Hz,$J_{9,10}$=7Hz, C-9),1.90(3H,d,J=7.5Hz,C-12),1.01 (3H,d,J=7Hz,C-10_1),1.00(3H,d,J= 7Hz,C-10_2)
 (E-isomer)			δ=9.55(1H,br,s,NH),5.90(1H,q,J=7.5 Hz,C-11),4.88(1H,dd,$J_{2,9}$=7.5Hz, $J_{2,NH}$=1.5Hz,C-2),2.54(3H,s,N-Ac), 2.20(3H,d,J=7.5Hz,C-12),1.89(1H, m,$J_{9,2}$=7.5Hz,$J_{9,10}$=7Hz,C-9),1.11 (3H,d,J=7Hz,C-10_1),0.98(3H,d,J= 7Hz,C-10_2)

TABLE VI (Cont.)

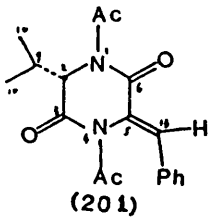
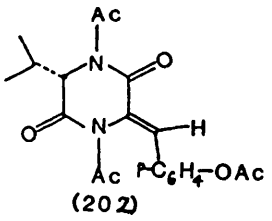
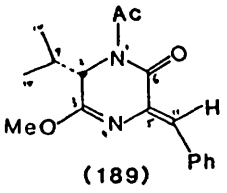
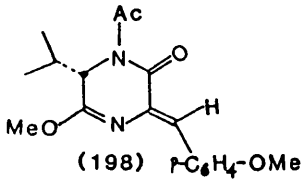
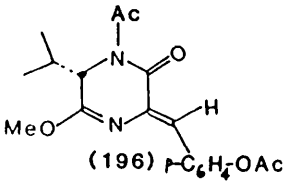
No of Compound and Structure	IR (cm^{-1})	MS	^{1}H-NMR (ppm)
 (201)	ν_{max}=1720,1690, 1620,1365,1230, 1165,1100	m/e=328(M^+, 6),286(76) 244(37), 201(100), 201(58), 173(12),116 (26),43(98)	δ=7.56(1H,s,C-13),7.38(5H,m,Ar-H),5.09(1H,d,J=10Hz,C-2),2.58(3H, s,C-8),2.47(3H,s,C-12),2.18(1H,m, C-9),1.17(3H,d,J=6.5Hz,C-10_1), 0.96(3H,d,J=6.5Hz,C-10_2)
 (202)	ν_{max}=1760, 1695,1625, 1595,1365, 1250,1190, 1165	m/e=386(M^+,1) 344(8),302(12) 217(13),156 121(27),43 (100)	δ=7.54(1H,s,C-13),7.37(2H,d,J= 8.5Hz,Ar-H),7.15(2H,d,J=8.5Hz, Ar-H),5.09(1H,d,J=10Hz,C-2), 2.59(3H,s,N-Ac),2.50(3H,s,N-Ac), 2.31(3H,s,O-Ac),2.14(1H,m,C-9), 1.15(3H,d,J=7Hz,C-10_1),0.95(3H, d,J=6.5Hz,C-10_2)
 (189)	ν_{max}=1690, 1645,1610, 1235,1195,	m/e=300(M^+,30) 258(12),215 (100),200(8), 181(79),43 (20)	δ=8.04-8.07(2H,m,o-Ar-H),7.31- 7.46(3H,m,Ar-H),7.27(1H,s,C-11), 5.03(1H,d,J=6Hz,C-2),3.97(3H,s, O-Me),2.61(3H,s,N-Ac),2.10(1H,m, J=7Hz,C-9),0.99(3H,d,J=7Hz,C-10_1),0.88(3H,d,J=7Hz,C-10_2)
 (198) p-C_6H_4-OMe	ν_{max}=1690, 1610,1645, 1225,1190	m/e=330(M^+,33) 280(5),246(18) 245(100),230 (6),202(3), 43(13),41(6)	δ=8.04(2H,d,J=9Hz,o-Ar-H),6.93 (2H,d,J=9Hz,m-Ar-H),7.25(1H,s, C-11),5.01(1H,d,$J_{9,2}$=6Hz,C-2), 3.96(3H,s,O-Me),3.85(3H,s,O-Me), 2.06(1H,m,$J_{9,2}$=6Hz,$J_{9,10}$=7Hz,C-9),2.60(3H,s,N-Ac), 0.98(3H,d,J= 7Hz,C-10_1),0.88(3H,d,J=7Hz,C-10_2).
 (196) p-C_6H_4-OAc	ν_{max}=1760, 1695,1650, 1600,1370, 1230,1195	m/e=358(M^+,2), 316(3),287(2), 259(5),245(36) 231(12),179(12) 150(10),136(31) 121(100),107 (36),43(72)	δ=8.08(2H,d,J=8.5Hz,o-Ar-H),7.24 (1H,s,C-11),7.13(2H,d,J=8.5Hz, m-Ar-H),5.02(1H,d,J=6Hz,C-2), 3.96(3H,s,O-Me),2.61(3H,s,N-Ac), 2.32(3Hz,s,O-Ac),2.08(1H,m,J=6Hz ,J=7Hz,C-9),0.98(3H,d,J=7Hz,C-10_1),0.87(3H,d,J=7Hz,C-10_2)

TABLE VI (Cont.)

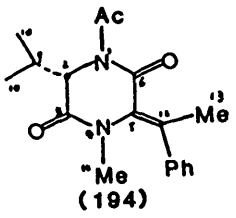
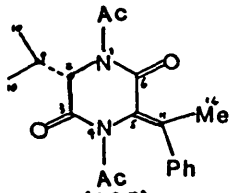
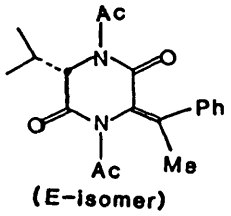
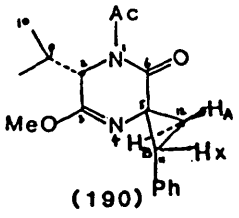
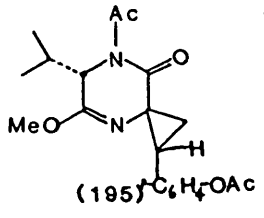
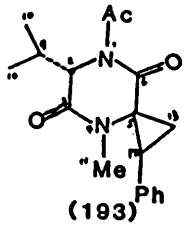
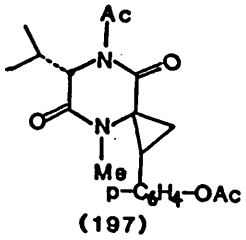
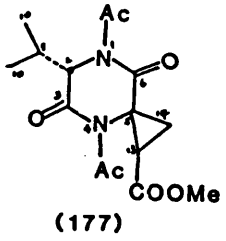
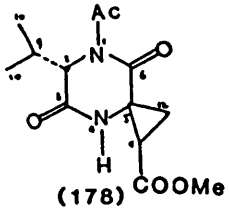
No of Compound and Structure	IR (cm^{-1})	MS	^1H-NMR (ppm)
 (194)	ν_{max}=1705-1675 (C=O),1610, 1440-1420,1365 1365,1320,1220	m/e=314(M^+, 100),272(95), 229(82),201 (42),145(34), 130(25),103 (35),83(50)	δ=7.42-7.30(3H,m,Ar-H),7.22-7.17 (2H,m,Ar-H),4.95(1H,d,J=11Hz,C-2),2.63(3H,s,N-Me),2.50(3H,s, N-Ac),2.47(3H,s,C-13),2.24(1H, 1.21(3H,d,J=6Hz,C-10_1),0.99(3H, d,J=6.5Hz,C-10_2)
 (203) (Z-isomer)	ν_{max}=1720,1670, 1620,1490,1410, 1365,1210	m/e=342(M^+, 12),300(42), 258(50),215 (100),201 (17),43(92)	δ=7.27-7.42(5H,m,Ar-H),5.05(1H, d,$J_{2,9}$=11Hz,C-2),2.61(3H,s,N-Ac),252(3H,s,N-Ac),2.31(1H,m,$J_{9,2}$ =11Hz,$J_{9,10}$=6.5Hz,C-9),2.08(3H, s,C-14),1.26(3H,d,J=6.5Hz),1.01 (3Hz,d,J=6.5Hz,C-10_2)
 (E-isomer)			δ=7.39-7.42(1H,m,Ar-H),7.09-7.15(4H,m,Ar-H),4.95(1H,d,$J_{2,9}$= 11Hz,C-2),2.52(3H,s,N-Ac),2.51 (3H,s,N-Ac),2.43(3H,s,C-14), 2.06(1H,m,$J_{9,2}$=11Hz,$J_{9,10}$=6.5Hz ,C-9),0.91(3H,d,J=6.5Hz,C-10_1), 0.59(3H,d,J=6.5Hz,C-10_2)
 (190)	ν_{max}=1690,1650 (C=O,C=N,st.), 1600,1490,1440 1430,1390,1370 1315,1240	m/e=314(M^+,39) 272(8),229 (100),43 (20),28(19)	δ=7.19-7.35(5H,m,Ar-H),4.88(1H, d,J=6Hz,C-2),3.50(3H,s,O-Me), 2.89(1H,dd,J_{XA}=8.5Hz,J_{XB}=10Hz, C-11),2.54(3H,s,N-Ac),2.38(1H, dd,J_{BA}=-5.5Hz,J_{BX}=10Hz,C-12_B), 1.89(1H,dd,J_{AB}=-5.5Hz,J_{AX}=8.5Hz ,C-12_A),1.87(1H,m,J=6Hz,7Hz,C-9),0.85(3H,d,J=7Hz,C-10_1),0.57 (3H,d,J=7Hz,C-10_2)
 (195)	ν_{max}=1760,1695 1655,1600,1505 1440,1370,1315 1240, 1195	m/e=372(M^+, 53),330(19), 287(100),245 (98),43(68)	δ=7.23(2H,d,J=9Hz,o-Ar-H),7.01 (2H,d,J=9Hz,m-Ar-H),4.90(1H,d, J=6.5Hz,C-2),3.50(3H,s,O-Me), 2.38(1H,dd,J_{XA}=10.5Hz,J_{XB}=8Hz, C-11),2.53(3Hz,s,N-Ac),2.37(1H, 1H,dd,J_{AX}=10.5Hz,J_{AB}=-5.5Hz, 12_A),2.28(3H,s,O-Ac),1.85(1H,dd ,J_{BX}=8Hz,J_{BA}=-5.5Hz,C-12_B), 1.82(1H,m,J=6.5Hz,J=7Hz,C-9),

TABLE VI (Cont.)

No of Compound and structure	IR (cm^{-1})	MS	^{1}H-NMR (ppm)
 (193)	ν_{max}=1695,1670 1590,1465,1420, 1365,1235	m/e=314(M^+, 80),272(100) ,229(65),201 (45),144(30) ,104(24),43 (56),28(27)	δ=7.13-7.37(5H,m,Ar-H),4.93(1H ,d,$J_{2,0}$=11.5Hz,C-2),2.85(3H,s, N-Me),2.64(1H,dd,J_{XA}=11Hz,J_{XB}= 8Hz,C-12),2.52(3H,s,N-Ac),2.51 (1H,dd,J_{AX}=11Hz,J_{AB}=-7Hz,C-13_A),2.19(1H,dd,J_{BX}=8Hz,J_{BA}=-7Hz, C-13_B),2.10(1H,m,J=11.5Hz,$J_{9,10}$ =6.5Hz,C-9),0.94(3H,d,J=6.5Hz, C-10_1),0.80(3H,d,J=6.5Hz,C-10_2).
 (197)	ν_{max}=1760,1700 -1640,1595, 1500,1370,1320 1240	m/e=372(M^+, ,66),330(7), 288(50),287 (43),259(15),245(23), 217(24),43 (100)	δ=7.17(2H,d,J=9Hz,Ar-H),7.08(2H ,d,J=9Hz,Ar-H),4.94(1H,d,J=11Hz ,C-2),2.84(3H,s,N-Me),2.62(1H, dd,J_{XA}=10.5Hz,J_{XB}=8Hz,C-12), 2.53(3H,s,N-Ac),2.52(1H,dd,J_{AX}= 10.5Hz,J_{AB}=-6Hz,C-13_A),2.29(3H, s,O-Ac),2.13(1H,dd,J_{BX}=8Hz,J_{BA}= -6Hz,C-13_B),2.07(1H,m,$J_{9,2}$=11Hz ,$J_{9,10}$=7Hz,C-9),0.94(3H,d,J=7Hz ,C-10_1),0.84(3H,d,J=7Hz,C-10_2)
 (177)	ν_{max}=1735-1670 (br,s,C=O),1635 1430,1370,1225, 1130,730	m/e=324(M^+, 282(18),241 (24),129(40) 240(17)	δ=4.98(1H,d,J=11Hz,C-2),3.87(3H ,s,O-Me),3.45(1H,dd,J_{XA}=9Hz,J_{XB} =6Hz,C-13),2.72(1H,dd,J_{AX}=9Hz, J_{AB}=-4Hz,C-14_A),2.15(1H,dd,J_{BX}= 6Hz,J_{BA}=-4Hz,C-14_B),2.10(1H,m, C-9),1.92(3H,s,N(4)-Ac),2.60(3H ,s,N(1)-Ac),1.04(3H,d,J=7Hz,C-10_1),0.62(3H,d,J=7Hz,C-10_2)
 (178)	ν_{max}=3220,1740 -1660,1730, 1220	m/e=282(M^+, 28),240(28) 156(32),124 (34),96(46) ,43(100), 28(42)	δ=7.12(1H,br.s,N-H),5.02(1H,d, J=11Hz,C-2),3.83(3H,s,O-Me), 3.69(1H,dd,J_{XA}=4Hz,J_{XB}=7Hz,C-11),2.59(3H,s,N-Ac),2.53(1H,dd, J_{AX}=4Hz,J_{AB}=-17Hz,C-12_A),2.12 (1H,m,C-12_B),2.10(1H,m,C-9), 1.15(3H,d,J=7Hz,C-10_1),0.98 (3H,d,J=7Hz,C-10_2)

EXPERIMENTAL FOR

PART TWO

The preparation of L-valine-N-carboxylic acid anhydride (136):

To a suspension of L-valine (4.68g, 40 mmol) in 60 ml of dry THF, 35 ml of phosgene solution in toluene (20%, 60mmol) was added dropwise at 40°C while stirring under an atmosphere of nitrogen. The vigorous stirring was continued (10 h) until the valine dissolved completely. After 2 hours purging with dry nitrogen , the solvent was removed by a rotary evaporator at 50°C. The residue was taken up in a little dry ethyl acetate, and the solvent once again removed by a rotary evaporator in vacuo (removal of hydrogen chloride). After 3 hours drying at room temperature in high vacuum, a white solid (5.65g,98.8%) was obtained and identified as the title compound from following data[85]:

IR : ν_{max} 3290(s,NH),2970-2980,1751,1620-1670,1365-1385cm^{-1}

^{1}H-NMR :

δ 7.26 (1H, br,s, NH), 4.26 (1H, d, C*-H), 1.94 (1H, m, CH), 1.04 (6H, m, Me).

MS (C.I.): 144(M + 1)$^+$, 116(M + 1 - CO)$^+$, 101(M + 1 - C_3H_7)$^+$.

Preparation of the compound (138) [L-Val-Gly-bislactam]

A solution of (136)(9.4g, 59 mmol) in THF(60 ml) was added dropwise to a vigorously stirred mixture of glycine ethyl

ester hydrochloride (8.22g, 59 mmol), triethylamine (18.8 ml, 135 mmol), and chloroform (freshly distilled, 75ml) at -78°C. After 3 hours stirring at -78°C and 30 minutes at room temperature, the triethylamine hydrochloride was separated off by suction, the solvent was removed by a rotary evaporator (< 60°C), and the residue was taken up in toluene (260ml, freshly distilled and sodium wire dried). The resulting solution and the suspension was heated for 12 hours under reflux with efficient mechanical stirring and then cooled to 0°C. The desired product (5.1g, 55.4%, m.p. 253-254°C, $[\alpha]^{20}_{D}$=20.2(C=0.9,water)) was obtained as a white solid after being washed several times with ether, and dried in high vacuo at room temperature for 3 days.

The preparation of triethyloxonium tetrafluoroborate :

Into a 1-l three-necked flask fitted with a stirrer, a dropping funnel, and a condenser fitted with a drying tube which had all been previously dried in an oven at 110°C(24 h), was placed 142g (126ml, 1 mole) of freshly distilled boron trifluoride etherate. Epichlorohydrin (freshly distilled, 70g, 59.5ml, 0.755moles) was added dropwise to maintain vigorous boiling. The mixture was refluxed an additional hour and allowed to stand at room temperature overnight. The stirrer was then replaced by a rubber cap and the supernatant ether solution was withdrawn from the crystalline mass of triethyloxonium fluoroborate with a syringe. Nitrogen was

admitted through a rubber cap during the operation to prevent moisture from entering the flask. The crystals were washed with portions (4 X 200ml) of sodium dried ether, and dried in vacuo. The white solid was dissolved in dry DCM. The reagent was stored in situ at $-10^{o}C$ and was used within a few days of preparation.

The preparation of (2R)-(-)-2,5-dihydro-3,6-diethoxy-2-isopropyl pyrazine (128):

To a flask (100ml) containing (138)(3.13g,20mmol) and a magnetic stirrer bar, triethyloxonium tetrafluoroborate solution (50ml, 1M solution in methylene chloride) was added dropwise with stirring under an atmosphere of argon. The reaction was carried out at RT,24h, then more triethyloxonium tetrafluoroborate (20ml, 1M solution in DCM) was added. The reaction was continued for another 3 days and followed by TLC (silica gel, pet. ether / EtOAc = 9:1). After addition of a solution of phosphate buffer [NaH_2PO_4-$2H_2O$ (28.1g, 0.18mol) and Na_2HPO_4-$2H_2O$ (106.8g, 0.6mol), in water (500ml)], the organic phase was separated and the aqueous phase was extracted (DCM, 3 X 20ml). The combined organic phase was dried over magnesium sulphate, the solvent was drawn off in vacuo, and the yellow oily residue was distilled. The product was obtained as a colourless oil (1.212g, 29%).

IR : ν_{max} 1685 (RO-C=N), 1308 and 1235 (=C-OR) cm^{-1}

^{1}H-NMR :

δ 4.03-4.24(4H, m, C-9, C-12), 3.96 (3H, m, C-2, C-5) 2.24(1H, m, C-7), 1.29(3H, t, J=7.0Hz, C-11,), 1.28(3H, t, J=7.0Hz, C-13), 1.03(3H, d, J=7.0Hz, C-8), 0.77(3H, d, J=7.0Hz, C-9).

MS: m/e=212(M)$^{+\cdot}$, 184(M - C_2H_4)$^{+\cdot}$, 169(M - C_3H_7)$^{+\cdot}$.

Elemental Analysis:

Found : C 57.8% ; H 8.59% ; N 12.4%.

Calculated for $C_{11}H_{20}N_2O_2$: C 57.9%; H 8.59%; N 12.3%.

Preparation of (2R)-(-)-2,5-dihydro-3,6-diethoxy-2-isopropyl-5-phenylthio pyrazine (139):

To a solution of L-Val-Gly-bislactim ethyl ether (128) (500mg, 2.35mmol) in THF(10ml) was added n-butyllithium solution (1.5ml,1.6M in hexane,2.4mmol) dropwise at -78^{o}C whilst stirring. The solution was maintained under nitrogen for 15 minutes at that temperature before the solution of phenyl disulfide (546 mg,2.5mmol in THF, 8ml) was added. The reaction was allowed to warm to room temperature over 5 hours while stirring. After the reaction, the solvent was evaporated by a rotary evaporator at 35^{o}C and the residue was extracted (EtOAc,50 ml). The organic phase was then washed 3 times with saturated sodium carbonate (10ml X 3), and dried over $MgSO_4$. After evaporation of the solvent and flash chromatography

(silica gel, pet. ether / EtOAc = 30:1) the desired product (a pair of diastereoisomers) was obtained as a nearly colourless oil (715mg, 78%) in the ratio, trans / cis = 5:1 (determined from its ^{1}H-NMR spectra).

IR : ν_{max} = 3060, 1675, 1640, 1305, 740 (-S-Ar) cm^{-1} .

^{1}H-NMR :

Trans isomer :

δ 7.22-7.45(5H,m,Ar-H), 5.19(1H,d,J=3.0Hz,C-2), 4.10-4.26 (4H,m, O-CH_2CH_3), 2.78(1H, dd ,J=3.0Hz, C-5), 2.13(1H,m, C-7), 1.29(6H, m, CH_2CH_3), 0.89(3H, d, J=7.0Hz, C-8), 0.54 (3H, d, J=7.0Hz, C-9).

Cis isomer:

δ 7.24-7.36(5H,m,Ar-H), 5.29(1H,d,J=4Hz, C-2), 4.07-4.25 (4H,m,-O-CH_2CH_3), 3.85(1H,dd,J=5.0Hz,J=4Hz,C-5),2.04(1H, m, J=5.0Hz,J=7.0Hz,C-7), 1.27(6H,m,CH_2CH_3), 1.04(3H,d, J=6.8Hz, C-8), 0.79(3H,d, J=6.8Hz, C-9).

MS(C.I.): 321$(M + 1)^+$, 211$(M - PhS)^+$, 169(211 - $C_3H_6)^+$, 141(169 - $C_2H_4)^+$.

Preparation of (2R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl -5-phenylthio pyrazine (140):

The same method as for the preparation of compound (139), was used starting from (2R)-(-)-2.5-dihydro-3,6-dimethoxy-2-iso-

propylpyrazine(128)(R=Me, 2ml, 11.18mmoles). After flash chromatography purification, a light yellow, strong smelling oil(3.15g,93%) was obtained and identified as the title compound (140)(a pair of diastereoisomers in the ratio trans/cis=5:3).

IR : ν_{max} 3055(Ar-H), 1675,1650,1305 (RO-C=N-),768, 743(-S-Ar) cm^{-1} .

^{1}H-NMR :

Cis isomer:

δ7.13-7.44(5H,m,Ar-H), 5.27(1H,d,J=4Hz,C-5), 3.86(1H,dd, J=4,7Hz,C-2), 3.69(3H,s,O-Me), 3.67(3H,s,O-Me), 1.97(1H,m, J=5,7Hz,C-7), 0.98(3H,d,J=7Hz,C-8), 0.68(3H,d,J=7Hz,C-9)

Trans isomer:

δ7.13-7.46(5H,m,Ar-H), 5.18(1H,d,J=3Hz,C-5), 3.71(3H,s,O-Me) , 3.66(3H,s,O-Me), 2.73(1H,dd, J=3,4Hz,C-2), 1.85(1H,m,J=4, 7Hz,C-7), 0.90(3H,d, J=7Hz,C-8), 0.52(3H,d,J=7Hz,C-9).

MS (C.I.) : 293(M + 1)$^+$, 183(M - PhS)$^+$, 141(183 - C_3H_6)$^+$.

Along with the major compound (140), another component was obtained in 5% yield which was purified by preparative TLC and identified as a disubstituted compound (142) [(2R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5,5-diphenyl-thiopyrazine]: It was characterized as follows:

IR: ν_{max}= 3060, 3030, 1670, 1650, 1305, 768, 740 cm^{-1}

^{1}H-NMR :

δ 7.13-7.56(10H,m,Ar-H), 3.73(3H,s,MeO(3)), 3.52(3H,s, MeO(6)), 2.69(1H,d,$J_{2,7}$=3.5Hz,C-2), 2.07(1H,m,$J_{7,2}$=3.5Hz, $J_{7,8}$=7Hz,C-7), 1.14(3H,d,J=7Hz,C-8_1), 0.72(3H,d,J=7Hz, C-8_2).

MS (C.I.): 401$(M + 1)^+$, 291$(M - PhS)^+$, 109$(PhS)^+$.

The yields and ratio of products of the reactions described in Table I (see discussion) were determined by internal- standard temperature controlled GLC analysis [120°C(5min.)--(10°C /min.)--240°C(5min.)--(20°C/min.)--280°C (10min.)].

Attempted reaction of (2R)-(-)-2,5-dihydro-3,6-diethoxy-2-iso -propyl pyrazine (128)(R = Me) with tosyl chloride

To a solution of (128)(R = Me, 33mg,0.156mmol) in THF (2ml), a solution of n-butyllithium (0.11ml of 1.6M solution in hexane, 1.1 equiv.) was added dropwise under argon at -78°C while stirring. After 10min. stirring, a solution of p-toluene-sulphonyl chloride (29.7mg, 0.156mmol) in THF (1ml) was added The reaction was carried out at -78°C for 4 hours and followed by TLC. After being warmed to room temperature and worked up as normal, 21mg (64%) of (128) was recovered from the reaction and no sulphonyl compound was isolated. The only new compound isolated (2.4mg, 7%) was identified as (141):

IR: ν_{max} 3035 (=C-H), 1330, 1260 and 1030 (N=C-OR) cm^{-1}

^{1}H-NMR:

δ 7.52(1H,s,C-5), 4.31(2H,t,J=7Hz,3-OCH_2-), 4.30(2H,t, J=7Hz,6-OCH_2-), 3.30(1H,qq,J=7Hz,C-7), 1.39(3H,t,J=7Hz, Me(3)), 1.38(3H,t,J=7Hz,Me(6)), 1.23(6H,d,J=7Hz,C-8) ppm.

MS : m/e = 210$(M)^{+\cdot}$, 195$(M - CH_3)^{+\cdot}$, 182$(C_9H_{14}N_2O_2)^{+\cdot}$.

Found: $M^{+\cdot}$ = 210.1359; Calculated for $C_{11}H_{18}N_2O_2$ $M^{+\cdot}$ = 210.1367.

The oxidation reaction of sulfide (140) with mCPBA under normal reaction conditions

To a solution of mCPBA (3.98g,23.1mmol) in DCM (40ml), was added a DCM (25ml) solution of the sulfide (140)(2.70g, 9.24mmol) at 0°C. The resulting mixture was warmed to RT (1h), stirred (17h) and quenched with NaOH(1ml of 1N) solution. After working up the solution as normal, the reaction was shown to have yielded a multi-component mixture. As well as the desired sulphone (144)(0.19g, 6%), several other components were also isolated as followed.

Component A (Rf=0.85, EtOAc/pet. ether =1:8) was isolated as colourless oil (0.97g, 58%) and identified as the aromatised compound (148):

IR : ν_{max} 1555, 1455, 1335 (C=N in aromatic ring), 1265, 1035, 1015 (C=C-OR) cm^{-1}

^{1}H-NMR :

δ 7.56(1H,s, C-5), 3.92(3H,s,3-OMe), 3.91(3H,s, 6-OMe), 3.14(1H,qq,J=7Hz, C-7), 1.24(6H,d,J=7Hz, C-8).

MS : m/e = 182$(M)^{+\cdot}$, 167$(M - CH_3)^{+\cdot}$, 139$(M - C_3H_7)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$, 28$(C_2H_4)^{+\cdot}$

Found: $M^{+\cdot}$ = 182.1045; Calculated for $C_9H_{14}N_2O_2$: $M^{+\cdot}$ = 182.1054

Component B (Rf = 0.7) was isolated as light yellow oil(80mg, 3%) and identified as compound (145):

IR : ν_{max} cm^{-1} 3060, 2850-2960, 1455(S-C), 1365, 1135, 1010

^{1}H-NMR :

δ 7.56(2H,m,o-Ar-H), 7.50(1H,m,p-Ar-H), 7.35(2H,m,m-Ar-H), 3.99(3H,s,O-Me), 3.52(3H,s,O-Me), 3.18(1H,qq,J=7Hz,7Hz,C-7), 1.19(6H,d,J=7Hz, C-8).

MS : m/e = 290$(M)^{+\cdot}$, 275$(M - CH_3)^{+\cdot}$, 260$(275 - CH_3)^{+\cdot}$, 218$(260 - C_3H_6)^{+\cdot}$, 109$(PhS)^{+\cdot}$

Found: $M^{+\cdot}$ = 290.1076; Calculated for $C_{15}H_{18}N_2O_2S$: $M^{+\cdot}$ = 290.1086.

Component C (Rf = 0.20) was isolated as a light yellow oil (0.16g, 5.4%) and identified as the compound (146):

IR : ν_{max} 3060(=C-H), 1540, 1455, 1335 (C=N in Aromatic ring), 1225(Ar-OR), 1420 and 1320(SO_2-Ar) cm^{-1}

^{1}H-NMR :

δ 8.05-8.12(2H,m,o-Ar-H), 7.51-7.68(3H,m,Ar-H), 4.03(3H, s,O-Me), 3.81(3H,s,O-Me), 3.30(1H,m,J=7Hz,C-7), 1.21(6H,d, J=7Hz,C-8).

MS: m/e = 322$(M)^{+\cdot}$, 141$(C_6H_9N_2O_2)^{+\cdot}$, 77$(Ph)^{+\cdot}$, 42$(C_3H_6)^{+\cdot}$, 28$(C_2H_4)^{+\cdot}$.

Found: $M^{+\cdot}$=322.0983; Calculated for $C_{15}H_{18}N_2O_2S$: $M^{+\cdot}$=322.0984.

Component D (Rf=0.17) was isolated as yellow oil (0.11g, 4%) and identified as the compound (147):

IR : ν_{max}3050, 2860-2960, 1550, 1450(S-C), 1365-1340, 1005(N-O) cm^{-1}

^{1}H-NMR :

δ 7.80(2H,m,o-Ar-H), 7.46(3H,m,Ar-H), 4.00(3H,s,O-Me), 3.87(3H,s,O-Me), 3.27(1H,qq, J=6.5Hz,C-7), 1.20(6H,d,J=6.5Hz, C-8).

MS : m/e = 306$(M)^{+\cdot}$, 197$(M - PhS)^{+\cdot}$, 182(197 - $CH_3)^{+\cdot}$, 167(182 - $CH_3)^{+\cdot}$, 109$(PhS)^{+\cdot}$, 77$(Ph)^{+\cdot}$.

Found: $M^{+\cdot}$ = 306.1032; Calculated for $C_{15}H_{18}N_2O_3S$: $M^{+\cdot}$ = 306.1037.

A repeat of the above reaction, but adding the reactants in the reverse order, produced a similar result.

Preparation of (2R)-(-)-2,5-Dihydro-3,6-diethoxy-2-isopropyl -5-phenylsulphonyl pyrazine (143)

To a solution of the sulfide (139)(32 mg,0.1mmol) in DCM(5ml), was added dropwise a solution of mCPBA(38mg,0.22 mmol) in DCM (2ml) at -78°C under an atmosphere of nitrogen whilst stirring. The reaction mixture was then warmed to room temperature while stirring(14h). After all of the starting material had disappeared, stirring was maintained for 2 more hours (RT), and then the white solid was filtered and washed with DCM (3 X 5ml). The filtrates were combined and washed with saturated sodium bicarbonate and further worked up as normal. A pale yellow oil (22.8mg, 65%) was isolated from flash chromatography (silica gel, DCM - ether) and identified as the title compound (143) by the following data:

IR : ν_{max} 3080(Ar-H), 1670 and 1630(RO-C=N-), 1420 and 1325(-SO_2Ar), 1305 and 1240(=C-OR) cm^{-1} .

^{1}H-NMR :

Trans isomer:

δ 7.88(2H,m,o-Ar-H), 7.66(1H,m,p-Ar-H), 7.55(2H,m, m-Ar-H), 5.28(1H,d,J=3Hz,C-5), 4.08-4.25(4H,m,O-CH-), 3.84(1H,dd,J=3, 3Hz,C-2), 2.30-2.45(1H,m,C-7), 1.25(3H,t,J=7Hz,-Me), 1.21(3H, t,J=7Hz,-Me), 1.04(3H,d,J=7.0Hz,C-8), 0.61(3H,d,J=7Hz,C-9).

Cis isomer:

δ 7.89(2H,m,Ar-H), 7.67(1H,m,Ar-H), 7.26(2H,m,Ar-H), 5.30 (1H,d,J=4.5Hz,C-5), 4.01-4.15 (4H,m,-O-CH-), 3.90(1H,dd, J=4.5 and 6Hz,C-2), 2.20-2.31(1H,m,C-7), 1.20-1.41(6H,m,Me),

1.10(3H,d,J=7Hz,C-8), 0.90(3H,d,J=7Hz,C-9).

MS(C.I.): 353$(M + 1)^+$, 211$(M - C_3H_6)^+$, 169(353 - C_3H_7 - $PhSO_2)^+$.

Preparation of (2R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl -5-phenylsulphonyl pyrazine (144)

Using the same method as for the preparation of compound (143) and starting from (140)(1.35g, 4.62mmol), the desired compound (144)(0.84g, 52%) was isolated as a pale yellow oil and characterized as follows:

IR : ν_{max} 3060, 1675, 1640, 1455, 1305 (-N=C-OR), 1435, 1420 and 1325 (R-SO_2Ar), 1260 (=C-OR) cm^{-1}

^{1}H-NMR (60MHz):

Major isomer: δ 7.6-8.2(1H,m,Ar-H), 5.4(1H,d,J=4.5Hz, C-5), 4.0(1H, dd,J=4.5 and 6Hz, C-2), 3.8(3H,s, O-Me), 3.7(3H,s, O-Me), 2.3(1H,m,J=6 and 7Hz, C-7), 1.1(3H,d, J=7Hz, C-8), 0.6(3H,d,J=7Hz, C-9).

MS (C.I.): 325$(M + 1)^+$, 183(325 - $PhSO_2)^+$, 141$(PhSO_2)^+$.

Compound (144) decomposes on storage at RT in $CHCl_3$, solution producing sulphinic acid[126] (mp:83° - 83.5°C). After 10 days under such conditions, no trace of compound (144) could be found. The only product isolated was (148).

Attempted C(5)-bromination reaction of (2R)-(-)-2,5-dihydro -3,6-dimethoxy-2-isopropyl pyrazine(128)(R = Me).

To a solution of (128)(R = Me, 0.09ml, 0.5mmol) in THF (5ml), was added dropwise a solution of n-BuLi (1.1equiv., 1.59M solution of hexene) at -78°C under argon. After stirring for 15min.(-78°C), the yellow solution of the carbanion was quenched with Br_2 (0.1ml) and the resulting mixture was stirred (1h, -78°C) before it was quenched with aqueous sodium metabisulfide(10ml, saturated solution) and followed by the normal work-up. A multi-component mixture resulted and no trace of the desired C-5-bromo product could be found by GC-MS analysis of the crude product. Two isomeric products were isolated and these were identified as the dimerised compounds (152)(34%, 31mg) and (153)(12%, 11mg).

The compound (152) was characterized as follows:

IR : ν_{max} 2850-2960, 1685(C=O), 1455, 1430, 1230, 1190, 1010 cm^{-1}

^{1}H-NMR :

δ 4.53(2H,dd,$J_{5,5'}$=2.5Hz, $J_{5,2}$=$J_{5',2'}$=3.5Hz,C-5,C-5'), 3.89(2H,dd, $J_{2,7}$=$J_{2',7'}$=3.5Hz, $J_{2,5}$=$J_{2',5'}$=3.5Hz, C-2, C-2'), 3.75(6H,s,6-OMe and 6'-OMe), 3.54 (6H,s,3-OMe and 3'-OMe), 2.25(2H,m,C-7 and C-7'), 1.06(6H,d,J=7Hz,C-8 and C-8'), 0.67(6H,d,J=7Hz,C-9 and C-9').

MS(C.I.) :

367$(M + 1)^+$, 183$(C_9H_{15}N_2O_2)^+$, 141(183 -

$C_3H_6)^{+\cdot}$.

Found: $M^{+\cdot}$ = 366.2285; Calculated for $C_{18}H_{30}N_4O_4$:

$M^{+\cdot}$ = 366.2265.

The compound (153) are characterized as follows:

IR : ν_{max} 1686, 1455, 1430 ,1230 , 1190, 1010 cm^{-1}

^{1}H-NMR :

δ 4.58(1H, dd, $J_{5,5'}$=2.5Hz, $J_{5,2}$=4Hz, C-5) , 4.46 (1H, dd, $J_{5',5}$=2.5Hz, $J_{5',2}$=6.5Hz, C-5′), 3.95 (1H, dd, $J_{2,5}$=4Hz, $J_{2,7}$=4Hz, C-2), 3.85 (1H, dd, $J_{2',5'}$=6.5Hz, $J_{2',7'}$=4Hz, C-2′), 3.67 (3H, s, OMe), 3.643 (3H, s, OMe), 3.637 (3H, s, OMe), 3.62 (3H, s, OMe), 2.28 (2H, m, $J_{7,2}$=$J_{7',2'}$=4Hz, $J_{7,8}$ = $J_{7',8'}$=7Hz, C-7, C-7′), 1.10 (3H, d, J=7Hz, C-8), 1.05 (3H, d, J=7Hz, C-8′), 0.71 (3H, d, J=7Hz, C-9), 0.69 (3H, d, J=7Hz, C-9′).

MS: m/e = 366$(M)^{+\cdot}$, 183$(C_9H_{15}N_2O_2)^{+\cdot}$, 141(183 - $C_3H_6)^{+\cdot}$.

Found: $M^{+\cdot}$ = 366.2285; Calculated for $C_{18}H_{30}N_4O_4$:

$M^{+\cdot}$ = 366.2265.

Nucleophilic reaction of (143) with acrolein

To a THF (3ml) solution of the sulphonyl compound (143)(76mg, 0.216mmol), was added dropwise a n-butyllithium solution (0.315ml of 1.6M solution in pentane, 0.216mmol) under nitrogen at -78°C with stirring. The stirring was continued for 10 minutes before the acrolein solution (0.216mmol in 1 ml

of THF) was added dropwise at that temperature. After being stirred at -78°C for 2 hours, the reaction mixture was diluted with ethyl acetate (40ml) and worked up as usual. The major component was isolated (17.8 mg, 20%) as a pale yellow oil and identified as the 1,2 addition product (155) from following data:

IR : ν_{max} 3460(OH), 3080(ArH), 1675 and 1645(O-C=N) cm^{-1}

^{1}H-NMR :

δ 7.88-8.00 (2H,m,Ar-H), 7.58-7.68(1H,m, Ar-H), 7.45-7.55 (2H,m,ArH), 5.40-5.56(1H,m, C-11), 5.21-5.32(1H,m,C-12_A), 5.01-5.19(1H,m,C-12_B), 3.95-4.34(4H,m,O-CH-), 3.88(1H,m,C-2), 3.05 and 2.84(1H,d,J=10.5Hz, C-10 two isomers), 5.01-5.40 (1H,br.s,OH), 2.30-2.50(1H,m,C-7), 1.17-1.43(6H,m,Me), 1.16 and 0.84, 1.04 and 0.55(6H,d,J=7Hz,C-8 and C-9 of isomers).

MS(C.I.): 408(M + 1)$^+$, 353(408 - C_3H_3O)$^+$, 267(408 - $PhSO_2$)$^+$, 211(267 - C_3H_4O)$^+$, 169(211 - C_3H_6)$^+$.

<u>The addition of sulphonyl compound (143) to acrolein using CuI</u>

To a solution of sulfonyl bislactim (143) (302.3mg, 0.859 mmol) in THF (10ml) was added dropwise an LDA solution (0.954 mmol, freshly made by using one to one equivalent of n-butyllithium and diisopropylamine at 0°C) at -78°C with stirring under nitrogen. The resulting mixture was stirred (-78°C,30min) and quickly transferred to another flask, containing 89.98 mg of CuI (freshly made and dried under vacuo

for 5 days), via a cannula. The reaction mixture was left to stand at -78°C for one hour before the acrolein solution (0.902mmol, in 4ml of THF) was added dropwise. The stirring was continued for a further 3 hours under nitrogen whilst the reaction mixture warmed to room temperature. After standing at room temperature for another 12 hours under nitrogen, saturated ammonium chloride solution was added, the solution was then extracted with ethyl acetate (15ml X 5) and further worked up as normal. Only one major component was isolated and was identified as compound (141)(p.237)(53mg, 29%). No desired cyclopropane amino acid derivatives could be detected.

Preparation of N,N´-dibenzyl-2-isopropyl piperazine-3,6-di -one (162) from (138)

To a solution of (138)(1.56g, 10mmol) in DMF(25ml), was added NaH(1.1equiv., 22mmol) whilst stirring at 0°C. After stirring until no more hydrogen was evolved (1h,0°C), the benzyl bromide (2.38ml, 20mmol) was added dropwise and the reaction temperature was allowed to rise up to room temperature over 6 hours whilst stirring. After the reaction mixture was worked up as normal and the crude product recrystallized from hot pet.ether (60-80°C), a white solid was obtained (2.88g, 86%), and identified as the title compound (162) from the following data:

IR : ν_{max} 3060, 3025, 1650 (C=O), 1435, 1345, 1325, 1290, 1165, 725, 700 cm^{-1}.

^{1}H-NMR :

δ 7.18-7.37 (10H, m, Ar-H), 5.37 (1H, d, $J_{A,B}$=C-7_A) 4.81 (1H, d, $J_{A,B}$=14.5Hz, C-11_A), 4.29 (1H, d, $J_{B,A}$ =14.5Hz, C-11_B), 3.97 (1H, d, J_{AB}=17.5Hz, C-5_A), 3.91 (1H, d, J_{BA}=17.5Hz, C-5_B), 3.77 (1H, d, $J_{2,8}$= 6.5Hz, C-2), 2.21 (1H, m, $J_{2,8}$=6.5Hz, $J_{8,9}$=7Hz, C-8), 1.09 (3H, J=7Hz, C-9), 0.92 (3H, d, J=7Hz, C-10).

MS : m/e = 336$(M)^{+\cdot}$, 293$(M - C_3H_7)^{+\cdot}$, 91$(PhCH_2)^{+\cdot}$.

Elemental Analysis:

Found: C 75.0%; H 7.22%; N 8.29%.

Calculated for $C_{21}H_{24}N_2O_2$:

C 75.0% ; H 7.14%; N 8.33%.

Preparation of (2R)-(-)-N,N´-dibenzyl-2-isopropyl-5-methyl piperazine-3,6-dione (163) from (162).

To a solution of (162)(168mg, 0.5mmol) in THF (5ml), was added dropwise a solution of n-BuLi (0.31ml of 1.6M solution in hexane, 0.5mmol) at -78^{o}C whilst stirring under argon. The reaction mixture was continuously stirred (-78^{o}C, 0.5h), then a solution of iodomethane (0.19ml, 6equiv.) in THF (2ml) was added dropwise at that temperature. After stirring (6h, -78^{o}C), the reaction mixture was worked-up as normal and the crude product was recrystallized from pet.ether 60^o-80^{o}C. A white solid was obtained (150mg, 85.7%) and identified as the title compound (163). The results of a ^{1}H-NMR spectrum showed that the product was the trans

isomer. As the cis isomer could not be seen from ^{1}H-NMR, it was assumed that the ratio of trans/cis was greater than 20:1.

Compound (163) is characterized as follows:

IR : ν_{max} 3060, 3030, 2850-2960, 1645 (C=O), 1435, 1355, 1290, 1255, 1170, 730, 700 cm^{-1}

^{1}H-NMR :

δ 7.19-7.39 (10H, m, Ar-H), 5.45 (1H, d, J_{AB}=15Hz, C-7_A), 5.35(1H, d, J_{AB}=15Hz, C-11_A), 4.16 (1H, d, J_{BA}=15Hz, C-7_B), 4.06 (1H, q, J=7Hz, C-5), 3.94 (1H, d, J_{BA}=15Hz, C-11_B), 3.81(1H,d,J=5Hz, C-2), 2.31 (1H, m, J=5Hz, 7Hz, C-8), 1.59 (3H, d, J=7Hz, C-12), 1.13 (3H, d, J=7Hz, C-9), 0.95 (3H, d, J=7Hz, C-10).

MS : m/e = 350$(M)^{+\cdot}$, 307$(M - C_3H_7)^{+\cdot}$, 91$(PhCH_2)^{+\cdot}$.

Elemental Analysis:

Found : C 75.7%; H 7.43%; N 7.90%.

Calculated for $C_{22}H_{26}N_2O_2$:

C 75.4%; H 7.43% ; N 8.00% .

Preparation of (2R)-(-)-N,N´-dibenzyl-2-isopropyl-5-phenyl thio-piperazine-3,6-dione (164)

To a solution of LDA (2.06mmol, freshly made from diisopropyl amine and n-BuLi in THF at 0^{o}C), was added dropwise a solution of (162)(0.629g, 1.87mmol) at -78^{o}C under argon. The reactants were stirred for 1 hour before a solution of

phenyl disulfide (408mg, 1.87mmol), in THF(3ml) was added at that temperature. The reaction was then stirred (3 h, -78°C; 4 h, RT) and worked up as normal. A crude product (0.81g, 97.6%) was obtained after filtration through a short column (silica gel), pure enough (shown from ^{1}H-NMR) for the oxidation step without further purification.

To further purify the crude product (100mg) a flash column was used. Pure (164) was isolated (81mg) in the yield of 81% and characterized as follows:

IR : ν_{max} 3030, 3060, 1655(C=O), 1575(ArC-C), 1435(C-S), 1250, 1165, 735, 690 cm^{-1}

^{1}H-NMR : (Trans isomer)

δ 7.68(2H,m,o-SAr-H), 7.67(3H,m,SAr-H), 7.10-7.34 (10H,m,Ar-H), 5.41(1H,d,J_{AB}=15Hz, C-7_A), 5.39(1H,d,J=15Hz, C-12_A), 4.96(1H,s,C-5), 3.98(1H,d,J_{BA}=15Hz,C-7_B), 3.92(1H, d,J_{BA}=15Hz,C-12_B), 3.71(1H,d,J=7.5Hz,C-2), 2.31(1H,m,J=7.5 and 7Hz,C-8), 1.19(3H,d,J=7Hz,C-9), 1.13(3H,d,J=7Hz,C-10).

MS (C.I.) : 445$(M + 1)^+$, 335$(M - PhS)^+$, 109$(PhS)^+$, 91$(PhCH_2)^+$.

Elemental Analysis:

Found: C 73.1% ; H 6.18% ; N 6.25%.

Calculated for $C_{27}H_{28}N_2O_2S$:

C 73.0% ; H 6.31% ; N 6.31%.

Another component (5mg, 4%) was isolated as a light yellow oil

and identified as the disubstituted compound (165):

IR : ν_{max} 3060, 3030, 1655(C=O), 1575, 1435(C-S), 1250, 1165, 735, 690 cm^{-1}

^{1}H-NMR :

δ 7.70-6.82(20H,m,Ar-H), 5.62(1H,d,J_{AB}=14.5Hz,C-7_A), 4.60 (2H,s,C-11), 4.45(1H,d,J_{BA}=14.5Hz,C-7_B), 3.76(1H,d,$J_{2,8}$= 5Hz,C-2), 2.19(1H,m,$J_{8,2}$=5Hz and $J_{8,9}$=7Hz,C-8), 0.95(3H,d, J=7Hz, C-9), 0.64(3H,d,J=7Hz,C-10).

Elemental Analysis:

Found : C 71.6% ; H 5.98% ; N 5.06%.

Calculated for $C_{33}H_{32}N_2O_2S_2$:

C 71.7% ; H 5.80% ; N 5.07%.

The preparation of N,N´-dibenzyl-2-isopropyl-5-phenyl sulphonyl piperazine-3.6-dione (158) from (164)

To a suspension of mCPBA (1.24g, 2.68mmol) in DCM(20ml), was added dropwise a solution of crude sulfide (164) (0.541g, 1.22mmol) in DCM (5ml) at -78°C. The reaction mixture was warmed to RT with stirring (5h) and the reaction followed by TLC. After the usual work-up and recrystallization from pet. ether (60°-80°C), a white solid (89.5%, 520mg) was isolated and identified as the title compound (158) from the following data:

IR : ν_{max} 3060, 3030, 1665, 1575, 1440, 1420, 1145

($ArSO_2R$) cm^{-1}

^1H-NMR (trans isomer):

δ 7.25-7.98(5H, m, Ar-H), 7.30(6H, m, Ar-H), 7.05(4H, m, Ar-H), 5.72(1H, d, J=15Hz, C-7_A), 5.44(1H, d, J=15Hz, C-11_A), 5.08(1H, s, C-5), 4.13(1H, d, J=15Hz, C-7_B), 3.93(1H, d, J=15Hz, C-11_B), 3.67(1H,d,J=9.5Hz, C-2), 2.65(1H,m,J=9.5Hz and J=7Hz, C-8), 1.25(3H, d, J=7Hz, C-9), 1.22(3H, d, J=7Hz, C-10).

MS (C.I.): 477$(M + 1)^+$, 335$(M + 1 - PhSO_2)^+$, 91$(PhCH_2)^+$.

Ratio of trans / cis = 20 : 1

Elemental Analysis:

Found: C 68.0% ; H 5.74% ; N 5.79%.

Calculated for $C_{27}H_{28}N_2O_4S$:

C 68.1% ; H 5.88% ; N 5.88%.

Another component (Rf=0.35, pet.ether/EA=15:1) was also isolated (25mg, 4%) and identified as the disulphonyl compound (166):

IR : ν_{max} 3060, 3030, 2850-2965, 1670, 1570, 1435(d), 1385-1360, 1330, 1195 cm^{-1}

^1H-NMR :

δ 7.41-8.10(10H, m, -SO_2-ph), 7.23-7.37(10H, m, Ar-H), 5.41(1H, d, J_{AB}=15Hz, C-7_A), 4.97(2H, s, C-11), 4.07(1H, d, J_{BA}=15Hz, C-7_B), 4.00(1H, d, $J_{2,8}$=4Hz, C-2), 2.24(1H, m, $J_{8,2}$=4Hz and $J_{8,9}$=7Hz,

C-8), 0.96(3H, d, J=7Hz, C-9), 0.62(3H, d, J=7Hz, C-10).

^{13}C-NMR :

δ 169.9(C=O of C-6), 166.7(C=O of C-3), 157.1 and 153.6 (C-1 of $-SO_2$-Phs), 136.3 and 135.1 (C(1) of two -Ph), 133.6, 131.4, 130.1, 129.73, 129.67, 129.12, 128.56, 128.50 and 128.21 (carbons of Ar), 131.1(C-5), 64.81(C-2), 48.49(C-7), 44.18(C-10), 31.99(C-8), 18.56(C-9), 15.93(C-10).

MS(C.I.): 618$(M + 1)^+$, 477$(M + 1 - PhSO_2)^+$, 335$(M - 2\ PhSO_2)^+$, 91$(PhCH_2)^+$.

Elemental Analysis:

Found: C 67.3%; H 5.26%; N 4.91%.

Calculated for $C_{33}H_{32}O_6S_2$:

C 67.3%; H 5.44%; N 4.76%.

m.p. 95.5° - 96.5°C

Attempted addition-elimination reaction between (158) and methyl acrylate under various conditions:

To a solution of the sulphone (158) (65.7mg, 0.13mmol) in THF (8ml), was added a solution of NaOMe (0.9ml of 1.7M solution, 1.5 equivalents) under argon at room temperature whilst stirring. After stirring (RT, 20min), the solution turned yellow, and methyl acrylate (0.138mmol) in THF (3ml) was then added. The reaction was carried out (RT, without sonic bath, 8h; with sonic bath,10h) and followed by TLC. Most of the starting compound remained unchanged and no desired product

could be identified.

Various other conditions were examined as follows:

(a) Et_3N/CCl_4, RT.(4hr.), 60^{o}-$65^{o}C$(10hr.)

(b) Et_3N/CCl_4, RT, Ultrasonic bath

(c) Ether-H_2O, KOH, $(Bu)_4N^{+}Cl^{-}$, 10hr. RT. with sonic bath, 2hr. at RT. with sonic bath

(d) Dioxane-H_2O, KOH, 5hr. RT.

(e) Ether/NaH 5hr. RT with sonic bath

(f) DME/^{t}BuOK-BuOH, 5hr. $70^{o}C$

Preparation of methyl bromoacrylate (167B)

This reagent was prepared according to a literature method[106], starting from methyl acrylate and bromine. The methyl dibromopropionate was achieved in quantitive yield in a 1 mole scale, and the methyl bromoacrylate was obtained in yield of 86.8% in a 100mmoles scale.

Attempted reaction between (128) and (167B)

To a solution of (128) (R=Me, 0.36ml, 2mmol), in THF(6ml), was added dropwise a solution of n-BuLi(1.32ml of 1.6M solution in hexane, 2.12mmol) at $-78^{o}C$ under argon whilst stirring. After stirring for (5h), a solution of methyl bromoacrylate (167B)(340mg, 2.12mmol) in THF(4ml) was added at that temperature (20 min) and the reaction was then carried out ($-78^{o}C$, 5h) before it was quenched with aqueous NH_4Cl and worked up. A multi-component mixture was generated from

the reaction and no desired cyclopropane (168) could be found from GC-MS study of the crude product. The major components were isolated (84mg, 9.7%) as a light-yellow oil and identified as compounds(173)(isomer 1) and (174) (isomer 2) from the following data:

IR : ν_{max} 3030(cyclopropane C-H), 2865-2960, 1740(C=O, st.), 1685(C=N, st.), 1430, 1380, 1350, 1305, 1235 cm^{-1}

^{1}H-NMR :

Isomer 1: δ 4.23(1H, ddd, J_{XA}=8Hz, J_{XB}=4.5Hz and $J_{2,5}$=4.5Hz, C-2), 3.97(1H, dd, $J_{5,2}$=4.5Hz and $J_{5,13}$=3Hz, C-5), 1.98(1H, dd, J_{AX}=8Hz and J_{AB}=14Hz, C-7_A), 3.00(1H, dd, J_{BX}=4.5Hz, J_{BA}=14Hz, C-7_B), 1.49(1H, d, J_{AB}=7Hz, C-10_A), 2.43(1H, d, J_{BA}=7Hz, C-10_B), 2.24(1H, m, $J_{13,5}$=3Hz and $J_{13,14}$=7Hz, C-13), 1.04(3H, d, J=7Hz, C-14), 0.69(3H, d, J=7Hz, C-15), 3.73(3H, s, OMe), 3.70(3H, s, OMe), 3.67(3H, s, OMe), 3.64(3H, s, OMe).

Isomer 2: δ 4.07(1H, ddd, J_{XA}=6Hz, J_{XB}=9Hz, and $J_{2,5}$=4.5Hz, C-2), 3.93 (1H, dd, $J_{5,2}$=4.5Hz and $J_{5,13}$=3Hz, C-5), 2.25(1H, dd, J_{AX}=6Hz and J_{AB}=14Hz, C-7_A), 2.68(1H, dd, J_{BX}=9Hz. and J_{BA}=14Hz, C-7_B), 1.41(1H, d, J_{AB}=7Hz, C-10_A), 2.50(1H, d, J_{BA}=7Hz, C-10_B), 2.24 (1H, m, $J_{13,5}$=3Hz and $J_{13,14}$=7Hz, C-13), 1.04(3H, d, J=7Hz, C-14), 0.69(1H, d, J=7Hz, C-15), 3.73(3H, s, MeO), 3.69 (3H, s, MeO), 3.64(3H, s, MeO), 3.62(3H, s, MeO).

MS (C.I.) : 433$(M + 1)^+$, 391$(M + 1 - C_3H_7)^+$, 141$(C_4H_8N_2O_2)^+$,

Attempted preparation of compound (168) by employing t-BuOK as base and (128) and (157B) as starting materials

Method A :

To a solution of (128)(0.36ml, 2mmol.) in THF(10ml) was added a solution of t-BuOK (2.2ml of 0.9M solution, 2mmol). After stirring ($0^{o}C$,RT), a solution of (157B)(2mmol) in THF (10ml) was added dropwise at that temperature. The reaction mixture was then stirred ($0^{o}C$, 1h; RT, 24h which includes 3 hours with ultrasonic bath) and the attempted reaction monitored by TLC. No reaction was observed from TLC and ^{1}H-NMR(60MHz).

Method B:

Method A was repeated but using DMF as solvent instead of THF and carried out at $0^{o}C$(1h) and at RT(24h). After the usual work-up, the ^{1}H-NMR of the crude product and GC results showed that most of the starting material (128) remained unchanged and a small amount of new compounds appeared as indicated by TLC and GC. The mass spectrum of the crude product gave an $M^{+\cdot}$ for (168) at 268(1%) which indicated that a certain amount of the spiro compound (168) was possibly obtained. As the conversion was extremely poor, no further effort was given to the manipulation of the reaction conditions.

Preparation of the spiro-cyclopropane derivative (177) and (178) via cyclopropanation of the bislactam (175)

To a solution of (175)(1.17g, 4.88mmol) and (157B)(0.5ml, 5mmol) in 15ml of DMF, was added a solution of t-BuOK(5.4ml of 0.9M solution in t-BuOH, 4.9mmol) over a period of 40 min. at $0^{o}C$ under an atmosphere of N_2. The reaction was stirred ($0^{o}C$ to RT, 6 h), then quenched with aqueous NH_4Cl and worked-up as normal. A multi-component mixture was generated from the reaction. Along with the starting material (175B)(0.41g, 35%) recovered, a yellow oil (0.33g, 24%) was isolated and identified as a mixture of (177) and (178) in the ratio of 1:4 (determined by ^{1}H-NMR).

The compound (177) was characterized as follows:

IR : ν_{max} 1735-1670(br.s, C=O, st.), 1635, 1430, 1370, 1225, 1130, 730 cm^{-1}

^{1}H-NMR :

δ 4.98(1H, d, $J_{2,9}$=11Hz, C-2), 3.87(3H, s, OMe), 3.45(1H, dd, J_{XA}=9Hz and J_{XB}=6Hz, C-14), 2.72(1H, dd, J_{AX}=9Hz and J_{AB}=-4Hz, C-15_A), 2.15(1H, dd, J_{BX}=6Hz, and J_{BA}=-4Hz, C-15_B), 2.10(1H, m, C-9), 1.92(3H, s, N(4)-Ac), 2.60 (3H, s, N(1)-Ac), 1.04(3H, d, J=7Hz, C-10), 0.62(3H, d, J=7Hz, C-11).

MS: m/e=324$(M)^{+\cdot}$, 282$(M - C_2H_2O)^{+\cdot}$, 240(282 - $C_2H_2O)^{+\cdot}$.

Found : M^{+}=324.1324; Calculated for $C_{15}H_{20}N_2O_6$:

$M^+ = 324.1319$

The data of compound (178) are list below:

IR : ν_{max} cm^{-1} 3440(NH,st), 2850-2960, 1730, 1680, 1370, 1220

^{1}H-NMR :

δ 7.12(1H, br.s, N-H), 5.02(1H, d, $J_{2,9}$=11Hz, C-2), 3.83(3H, s, OMe), 3.69(1H, dd, J_{XA}=4Hz and J_{XB}=7Hz, C-12), 2.59 (3H, s, N-Ac), 2.53 (1H, dd, J_{AX}=4Hz and J_{AB} = -17Hz, C-13$_A$), 2.12(1H, dd, J_{BX} = 7Hz and J_{BA} = -17Hz, C-13$_B$), 2.10(1H, m, $J_{9,2}$=2Hz and $J_{9,10}$ = 7Hz, C-9), 1.15(3H, d, J = 7Hz, C-10), 0.98(3H, d, J = 7Hz, C-11).

MS : m/e = 282$(M)^{+\cdot}$, 240$(M - C_2H_2O)^{+\cdot}$, 198(240 - $C_3H_6)^{+\cdot}$, 96$(C_4H_4N_2O)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$.

Preparation of (2R)-N,N´-diacetyl-2-isopropyl piperazine-3,6-dione (183)

A mixture of (2R)-2-isopropyl piperazine-3,6-dione(138)(3.1g, 20mmol) and acetic anhydride(60ml) was stirred (130°-135°C, 12h),and then the solvents were evaporated. After the usual work-up, a yellow solid (4.75g, 99%) was obtained which was further purified (4.32g, 90%) by recrystallization from pet.ether (60°-80°C) / ether, and characterized as the title compound (183):

IR : ν_{max} 2870-2960, 1690(C=O), 1370 cm^{-1}

^{1}H-NMR :

δ 5.08(1H, d, J=19Hz, C-5_B), 4.99(1H, d, J=7Hz, C-2), 4.13(1H, d, J=19Hz, C-5_A), 2.59(3H, s, C-8), 2.57(3H, s, C-13), 2.08(1H, m, J=7Hz, C-9), 1.11(3H, d, J=7Hz, C-10), 0.99(3H, d, J=7Hz, C-11)

MS (Low eV EI) : m/e = 240$(M)^{+\cdot}$, 198$(M - C_2H_2O)^{+\cdot}$, 156(198 - $C_2H_2O)^{+\cdot}$, 114(156 - $C_3H_6)^{+\cdot}$.

Elemental Analysis:

Found: C 55.2% ; 6.81% ; N 11.7% .

Calculated for $C_{11}H_{16}N_2O_4$: C 55.0% ; 6.67% ; N 11.7% .

Preparation of N(1)-acetyl-5-benzylidene-2-isopropyl piperazine-3,6-dione (184)

To a solution of N,N'-diacetyl-bis(L-Val-Gly-)lactam (183) (1.2g, 5mmol.) and benzaldehyde(0.56ml, 5.5mmol.) in DMF(15ml), was added dropwise a solution of t-BuOK(6.1ml of 0.9M solution in t-BuOH, 1.1equiv.) at 0^{o}C under an atmosphere of nitrogen. The reaction mixture was warmed up to RT over 6 hours whilst stirring and then poured into water (150ml) and worked-up as normal. A light-yellow oil was obtained (1.34g, 94%) and identified as the title compound (184) from the following data:

IR : ν_{max} 3210(NH), 3070 and 3020(=C-H), 1690(C=O), 1620, 1365, 1225, 1200 cm^{-1}

^{1}H-NMR :

1365, 1225, 1200 cm^{-1}

^{1}H-NMR :

δ 8.33(1H, s, N-H), 7.35-7.45(5H, m, ArH), 7.15(1H, s, C-12), 4.97(1H, d, J=7Hz, C-2), 2.59(3H, s, N-Ac), 2.12(1H, m, J=7Hz, C-9), 1.06(3H, d, J=7Hz, C-10), 1.05(3H, d, J=7Hz, C-11).

MS : m/e=286$(M)^{+\cdot}$, 244$(M - C_2H_2O)^{+\cdot}$, 202$(244 - C_3H_6)^{+\cdot}$, 201$(244 - C_3H_7)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$.

Elemental Analysis:

Found : C 66.9% ; H 6.19% ; N 10.0%.

Calculated for $C_{16}H_{18}N_2O_3$:

C 67.1% ; H 6.29% ; N 9.79%.

The chiral lanthanide shift ^{1}H-NMR study on the product of the reaction showed that the ratio of two isomers (2R) and (2S) is 9:1product is about 80% ee.

For a repeat of the above reaction (10mmol) but using molar equiv. of t-BuOK, the product (184) was obtained in good yield (2.31g, 81%). As a result of only one isomer being observed from chiral lanthanide shift ^{1}H-NMR spectrum, we assume that the product is greater than 95% ee.

Preparation of (2R)-N(1)-acetyl-5-(4´-hydroxyphenyl--methylidene)-2-isopropyl-piperazine-3,6-dione (185)

Applying the same procedure as in the preparation of (184) and

starting from (183) (2.4g, 10mmol.) and 4-hydroxybenzaldehyde (1.39g, 11mmol.), a component (787mg, 26.1%) was isolated as a yellow oil and identified as the title compound (185) from the following data:

IR : ν_{max} 3370-3150(OH, N-H), 3070, and 3070(ar V-H), 2860-2965, 1760 and 1620(C=0),1595(ar C-C), 1365,1225 and 1195(Ar-6H), 1165, cm^{-1}

^{1}H-NMR :

δ 8.65(1H, br, s, OH), 7.95(1H, br.s, N-H), 7.60(1H, br.s, OH), 7.50(2H, d, J=9Hz, O-Ar-H), 7.25(2H, d, J=9Hz, m-ArH), 7.15(1H, s, C-12), 5.05(1H, d, $J_{2,9}$=7Hz, C-2), 2.65(3H, s, N-Ac), 2.10(1H, m, C-9), 1.25(3H, d, J=7Hz, C-10), 1.07(3H, d, J=7Hz, C-11)

MS : m/e=302$(M)^{+\cdot}$, 260$(M - C_2H_2O)^{+\cdot}$, 217(260 - $C_3H_7)^{+\cdot}$.

Preparation of 4-acetoxy benzaldehyde (188)

The acetylation reaction was carried out (RT, 14h) in an ethereal solution (100ml) and started from 4-hydroxy-benzaldehyde (3.66g, 30mmol), acetyl chloride (23.5ml, 33mmol) and pyridine (2.67ml,33mmol). After usual work-up , a light yellow oil (4.08g, 82.9%) was obtained and identified as the desired compound (188), which is in agreement with the literature data[127] b.p. 152-153^oC /17mm.

Preparation of N(1)-acetyl-5-ethylidene-2-isopropyl - piperazine-3,6-dione (187)

Using the same procedure as for the preparation of (186) and starting from (183)(1.2g,5mmol) and acetaldehyde (4equiv.), the E-and Z-isomer of (187)(1.07g, 95%) were obtained as an inseparable mixture (colourless oil) and characterized as follows:

IR : ν_{max} 3200(N-H), 3080, 2860-2965, 1695, 1675, 1640(C=O), 1365, 1230 cm^{-1}

^{1}H-NMR :

Z-isomer :

δ 9.35(1H, br.s, N-H), 6.41(1H, q, $J_{12,13}$=7.5Hz, C-12), 4.92(1H, dd, $J_{2,9}$=7.5Hz and $J_{2,N-H}$=1.5Hz, C-2), 2.53(3H,s,N-Ac),2.05(1H,m,$J_{9,2}$=7.5Hz and $J_{9,10}$=$J_{9,11}$=7Hz, C-9), 1.90(3H, d, $J_{13,12}$=7.5Hz, C-13), 1.01(3H, d, J=7Hz, C-10), 1.00(3H, d, J=7Hz, C-11)

E-isomer :

δ 9.55(1H, br.s, N-H), 5.90(1H, q, $J_{12,13}$=7.5Hz, C-12), 4.88(1H, dd, $J_{2,9}$=7.5Hz and $J_{2,N-H}$=1.5Hz, C-2), 2.54(3H, s, N-Ac), 2.20(3H, d, $J_{13,12}$=7.5Hz, C-12), 1.89(1H, m, $J_{9,2}$=7.5Hz and $J_{9,10}$=$J_{9,11}$=7Hz, C-9), 1.11(3H, d, J=7Hz, C-10), 0.98(3H, d, J=7Hz, C-11)

MS : m/e=224$(M)^{+\cdot}$, 182$(M - C_2H_2O)^{+\cdot}$, 140(182 - $C_3H_6)^{+\cdot}$, 139(182 - $C_3H_7O)^{+\cdot}$, 111(139 - $CO)^{+\cdot}$. 43$(C_3H_7)^{+\cdot}$

Found for mixture : $M^{+\cdot}$= 224.1159.

Calculated for $C_{11}H_{16}N_2O_3$: M^+ = 224.1159.

The ratio of Z-/E- = 19:2 detected from ^{1}H-NMR NOE at 9.35ppm(N-H), the corresponding position at 1.90ppm (C-12), showed that the major isomer is the compound in which the methyl group is in the Z relationship with N-H.

Attempted cyclopropane construction via Simmons-Smith Reaction

To a solution of (184)(1.28g, 4.48mmol) in ether(30ml) which contains Zn(Cu) powder(2.93g, freshly made), was added methylene diiodide(3.65ml, 45mmol, 10equiv.) and one small crystal of I_2. The reaction was gently heated whilst stirring (6h, under reflux in ether; 3h, with ultrasonic bath). After usual work-up and evaporation of low boiling liquids under vacuo, the starting material (1.21g, 95%) was recovered, but no cyclopropane was isolated.

Attempted cyclopropane construction via sulfoxonium ylide addition-elimination reaction

To a 50ml one-necked round bottomed flask containing trimethyl sulfoxonium iodide (242mg, 1.1mmol) and sodium hydride (1.1mmol) was added DMF (10ml) under argon whilst stirring at 0^{o}C. The mixture was then stirred until all of the trimethyl sulfoxonium iodide had disappeared, and then a solution of

(184)(1mmol) in DMF (2 ml) was added dropwise at that temperature and the reaction followed by TLC. After reacting for 5 hr. at RT, 10 hr. at 80°C and 1 hr. at 100°C, the reaction mixture was poured into water (80ml), extracted with ether and worked up as normal. A multi-component mixture was obtained from which none of the desired compound could be isolated.

Preparation of spiro[2-phenyl-cyclopropane-1,1´-N(3´)-acetyl-(4R)-4-isopropyl-5-methoxy-5´,6´-dehydro-piperazine-2´-one] (190) via diazomethane insertion

To a solution of (184)(286mg, 1mmol) in DMF(2ml), was added an ethereal (10ml) solution of diazomethane (slightly more than 1 mmol, freshly made from diazald and NaOH in a solution of ether-ethanol). The reaction mixture was stirred (RT, 50h) under nitrogen and the reaction followed by TLC. After working up as normal, a multi-component mixture was obtained . A major component 56.2mg, 16%) was isolated as a colourless oil (Rf=0.65, DCM) and characterized as compound (189) from the following data:

IR : ν_{max} 3050, 2850-2965, 1690, 1645, 1610, 1235, 1195 cm^{-1}.

^{1}H-NMR :

δ 8.06(2H, m, o-Ar-H), 7.31-7.46(3H, m, Ar-H), 7.27(1H, s, C-13), 5.03(1H, d, J=6Hz, C-2), 3.97(3H, s, OMe), 2.61(3H, s, N-Ac), 2.10(1H, m, J=7Hz, C-9), 0.99(3H, d, J=7Hz, C-10), 0.88(3H, d, J=7Hz, C-11)

MS : m/e=300$(M)^{+\cdot}$, 258$(M - C_2H_2O)^{+\cdot}$, 215$(258 - C_3H_7)^{+\cdot}$ 200$(215 - CH_3)^{+\cdot}$, 181$(258 - Ph)^{+\cdot}$,43$(C_3H_7)^{+\cdot}$.

Elemental Analysis:

Found : C 68.1% ; H 6.67% ; N 8.59% .

Calculated for $C_{17}H_{20}N_2O_3$:

C 68.0% ; H 6.67% ; N 8.33% .

Another major component was obtained as white crystals (Rf=0.60, DCM) in the yield of 21%(66.3mg) and identified as the title compound (190):

IR : ν_{max} 3090, 3040, 2850-2965, 1690, 1650(C=O, C=N, st), 1600, 1490, 1440, 1430, 1390, 1370, 1315, 1240 cm^{-1}

^{1}H-NMR :

δ 7.19-7.35(5H, m , Ar-H), 4.88(1H, d, J=6Hz, C-2), 3.50(3H, s, O-Me), 2.89(1H, dd, J=8.5Hz and J=10Hz, C-12), 2.54(3H, s, N-Ac), 2.38(1H, dd, J_{BA}=-5.5Hz and J=10Hz, C-13_B), 1.89(1H, dd, J=-5.5Hz and J_{AX}=8.5Hz, C-13_A), 1.87(1H, m, J=6.0 and 7.0Hz, C-9), 0.85(3H, d, J=7Hz, C-10), 0.57(3H, d, J=7Hz, C-11)

MS : m/e=314$(M)^{+\cdot}$, 272$(M - C_2H_2O)^{+\cdot}$, 229$(272 - C_3H_7)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$, 28$(C_2H_4)^{+\cdot}$.

Found: M^+=314.1621;

Calculated for $C_{18}H_{22}N_2O_3$: M^+= 314.1628.

m.p. 71.5° - 72°C

A repeat reaction on the 5 mmol. scale(1.43g) of (184) was carried out in more than 3 equiv. of diazomethane in ether solution. After the reaction was worked up as normal, the desired O-methylated cyclopropane derivative(190) was obtained

in the yield of 30%(472mg) together with another two compounds.

A compound (Rf=0.40, DCM, 420mg, 27%) was isolated and identified as the compound (194) from the following data:

IR : ν_{max} 3050, 2850-2965, 1705-1675(C=O), 1610, 1440-1420, 1365, 1320, 1220 cm^{-1}

^{1}H-NMR :

δ 7.42-7.37(3H, m, Ar-H), 7.22-7.17(2H, m, Ar-H), 4.95(1H, d, J=11Hz, C-2), 2.63(3H, s, N-Me), 2.50(3H, s, N-Ac), 2.47(3H, s, C-14), 2.24(1H, m, J=11 and J=6.5Hz, C-9), 1.21(3H, d, J=6.5Hz, C-10), 0.99(3H, d, J=6.5Hz, C-11)

MS:m/e=314$(M)^{+\cdot}$, 272$(M - C_2H_2O)^{+\cdot}$, 229$(272 - C_2H_7)^{+\cdot}$, 201$(229 - CO)^{+\cdot}$, 145$(C_9H_{11}N)^{+\cdot}$, 130$(145 - CH_3)^{+\cdot}$, 83$(C_3H_3N_2O)^{+\cdot}$

Elemental Analysis:

Found: C 68.7% ; H 7.06% ; N 8.72% .

Calculated for: $C_{18}H_{22}N_2O_3$:

C 68.8% ; H 7.01% ; N 8.92% .

Another component (Rf=0.30, DCM) was obtained (350mg, 22%) as white crystals and characterized as compound (193):

IR : ν_{max} 3030, 2850-2965, 1695, 1670(C=O, st.), 1590, 1465, 1420, 1365, 1235 cm^{-1}.

^{1}H-NMR :

δ 7.13-7.37(5H, m, Ar-H), 4.93(1H, d, $J_{2,9}$=11.5Hz, C-2), 2.95(3H, s, N-Me), 2.64(1H, dd, J_{XA}=11Hz and J_{XB}=8Hz, C-13), 2.52(3H, s, N-Me), 2.51(1H, dd, J_{AX}=11Hz and

J_{AB}=-7Hz,C-14_A), 2.10(1H,m,$J_{9,2}$=11.5Hz and $J_{9,10}$=6.5Hz, C-9), 0.94(3H, d, J=6.5Hz, C-10), 0.80(3H, d, J=6.5 Hz, C-11)

MS : m/e=314$(M)^{+\cdot}$, 272$(M - C_2H_2O)^{+\cdot}$, 229(272 - $C_3H_7)^{+\cdot}$, 201(229 - $CO)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$, 42$(C_3H_6)^{+\cdot}$, 28$(CO)^{+\cdot}$.

Elemental Analysis:

Found : C 68.6% ; H 6.97% ; N 8.86% .

Calculated for $C_{18}H_{22}N_2O_3$:

C 68.8% ; H 7.01% ; N 8.92% .

m.p. 133° - 134°C

Preparation of spiro[2-(4´´-acetoxyphenyl)-cyclopropane-1,1´-N(3´)-acetyl-(4R)-4-isopropyl)-5-methoxy-5´,6´-dehydro-piperazine-2´-one] (195) via diazomethane insertion

Applying the same procedure as was used for the preparation of (190) but starting from (186)(516mg, 1.5mmol.) with a slight excess of diazomethane, a multi-component mixture was generated.

The first component was isolated (10mg, 4.5%) as a light yellow oil and identified as (198):

IR : ν_{max} 3030-3080, 1765, 1690, 1645, 1610-1595, 1500 cm^{-1}

^{1}H-NMR :

δ 8.04(2H, d, J=9Hz, o-Ar-H), 6.93(2H, d, J=9Hz, m-Ar-H), 7.25(1H, s, C-12), 5.01(1H, d, $J_{2,9}$=6Hz,C-2), 3.96(3H, s, O-Me),

C-9), 0.98(3H, d, J=7Hz, C-10), 0.88(3H, d, J=7Hz, C-11)

MS : m/e=330$(M)^{+\cdot}$, 245$(M - C_2H_2O - C_3H_7)^{+\cdot}$,

230$(245 - CH_3)^{+\cdot}$, 202$(230 - CO)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$.

Found : $M^{+\cdot}$ = 330.1558

Calculated for $C_{18}H_{22}N_2O_4$: 330.1577

The second component was obtained (24mg, 10%) as a light yellow oil and identified as the O-methylated product (196):

IR : ν_{max} 3030-3070,1760,1685,1640,1605-1590,1490 cm^{-1}.

^{1}H-NMR :

δ 8.08(2H, d, J=8.5Hz, o-Ar-H), 7.24(1H, s, C-12), 7.13(2H, d, J=8.5Hz, m-Ar-H), 5.02(1H, d, J=6Hz, C-2), 3.96(3H, s, O-Me), 2.61(3H, s, N-Ac), 2.32(3H, s, O-Ac), 2.08(1H, m, J=6 and 7Hz, C-9), 0.98(3H, d, J=7Hz, C-10), 0.87(3H, d, J=7Hz, C-11)

MS : m/e=358$(M)^{+\cdot}$, 316$(M - C_2H_2O)^{+\cdot}$, 274$(316 - C_2H_2O)^{+\cdot}$,

231$(274 - C_3H_7)^{+\cdot}$, 136$(C_8H_8O_2)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$

Found : $M^{+\cdot}$ = 358.1517

Calculated for $C_{19}H_{22}N_2O_5$: $M^{+\cdot}$ = 358.1527

The third component (52mg, 21%) was separated as a colourless oil and characterized as the desired compound (195):

IR : ν_{max} 3090, 3030, 2850-2965, 1760(C=O of ester), 1695, 1655(C=O,C=N,st.),1600,1505,1440,1370,1315,1240,1195 cm^{-1}

^{1}H-NMR :

δ 7.23(2H, d, J=9Hz, o-Ar-H), 7.01(2H, d, J=9Hz, m-Ar-H), 4.90(1H, d, J=6.5Hz, C-2), 3.50(3H, s, O-Me), 2.88(1H, dd, J=10.5Hz and J=8Hz, C-12), 2.53(3H, s, N-Ac), 2.37(1H,dd,

J=10.5Hz and J=-5.5Hz, C-13_A), 2.28(3H, s, O-Ac), 1.85(1H, dd, J=8Hz and J=-5.5Hz, C-13_B), 1.82(1H, m, J=6.5Hz, 7Hz, C-9), 0.85(3H, d, J=7Hz, C-10), 0.59(3H, d, J=7Hz, C-11)

MS : m/e=372$(M)^{+\cdot}$, 330$(M - C_2H_2O)^{+\cdot}$, 287$(M - C_3H_7)^{+\cdot}$, 245$(M - C_2H_2O)^{+\cdot}$, 43(C_3H_7)

Found : $M^{+\cdot}$ = 372.1683

Calculated for $C_{20}H_{24}N_2O_5$: $M^{+\cdot}$ = 372.1683

The last component was isolated (45mg, 18%) and identified as the N-methylated spiro-cyclopropane product(197):

^{1}H-NMR :

δ 7.17(2H, d, J=9Hz, Ar-H), 7.08(2H, d, J=9Hz, Ar-H), 4.94(1H, d, $J_{2,9}$=11Hz, C-2), 2.84(3H, s, N-Me), 2.62(1H, dd, J_{XA}=10.5Hz, J_{XB}=8Hz, C-13), 2.53(3H, s, N-Ac), 2.52(1H, dd, J_{AX}=10.5Hz, J_{AB}=-6Hz, C-14_A), 2.13(1H, dd, J_{BX}=8Hz, J_{BA}=-6Hz, C-14_B), 2.07(1H, m, J=11Hz, J=7Hz, C-9), 0.94(3H, d, J=7Hz, C-10), 0.84(3H, d, J=7Hz, C-11).

MS : m/e=372$(M)^{+\cdot}$, 330$(M - C_2H_2O)^{+\cdot}$, 288$(330 - C_2H_2O)^{+\cdot}$, 287$(330 - C_3H_7)^{+\cdot}$, 259$(287 - CO)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$.

Found : M^+= 372.1667 ; Calculated for $C_{20}H_{24}N_2O_5$: M^+=372.1683 .

m.p. 126.5° - 127°C

Preparation of N(1)-acetyl-2-isopropyl-5-spiro-[11-methyl-(5-11-12)cyclopropyl]-piperazine-3,6-dione (199)

Applying the same procedure and using (187)(784mg, 3.5mmol.)

IR : ν_{max} = 3060, 3030, 2850-2965, 1720(C=0), 1670, 1620, 1490 ,1365, 1210 cm^{-1}

^{1}H-NMR : Z isomer:

δ 7.27-7.42(5H, m, Ar-H), 5.05(1H, d, $J_{2,9}$=11Hz, C-2), 2.61(3H, s, N_4-Ac), 2.52(3H, s, N_1-Ac), 2.31(1H, m, $J_{9,2}$ = 11Hz, $J_{9,10}$ = 6.5Hz, C-9), 2.08(3H, s, C-15), 1.26(3H,d, J = 6.5Hz, C-10), 1.01(3H, d, J = 6.5Hz, C-11)

MS : m/e = 342$(M)^{+\cdot}$, 300$(M - C_2H_2O)^{+\cdot}$, 258(300 - $C_2H_2O)^{+\cdot}$, 215(258 - $C_3H_7)^{+\cdot}$, 43$(C_3H_7)^{+\cdot}$.

E isomer:

δ 7.39-7.42(1H, m, Ar-H), 7.09-7.15(4H, m, Ar-H), 4.95(1H, $J_{2,9}$=11Hz, C-2), 2.52(3H, s, N(1)-Ac), 2.51(3H, s, N(A)-Ac)), 2.43(3H, s, C-15), 2.06(1H, m, $J_{9,2}$=11Hz, $J_{9,10}$=6.5Hz,C-9), 0.91(3H, d, J=6.5Hz, C-10), 0.95(3H, d, J=6.5Hz, C-11).

Found : M^+=342.1572

Calculated for $C_{19}H_{22}N_2O_4$ M^+ =342.1578

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REGIO- AND DIASTEREOSELECTIVITY IN ALDOL REACTIONS OF CYCLOPENT-2-ENONE, 2-(5H)FURANONE AND THEIR DERIVED TRIMETHYLSILYLOXYDIENES

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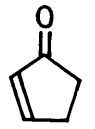
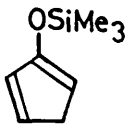
School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY.

Summary: Differences in erythro/threo-selectivity were assessed for aldol condensations of aldehydes with the lithium salts of cyclopent-2-enone,2-(5H)furanone, and for Lewis acid catalysed condensations with the derived trimethylsilyoxydienes.

Aldol reactions of the anion from cyclopentenone (1) have not been systematically assessed. Earlier studies showed that lithium diisopropylamide mediated alkylations were problematical,[1] and suggested that a 3-substituent was desirable for the avoidance of self-condensation processes. We therefore report further studies of the parent system (1) and the derived trimethylsilyloxy diene (2), together with interesting comparisons and differences from the chemistry of (3) and its silyl ether (4).



(1)



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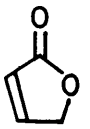

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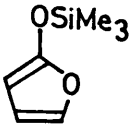

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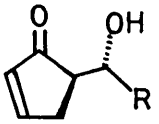
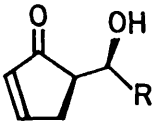
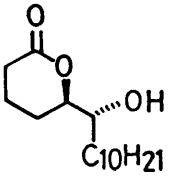


(5a) R = Me
(5b) R = Et
(5c) R = ^{i}Pr
(5d) R = $PhCH_2$
(5e) R = $C_{10}H_{21}$



(6a)
(6b)
(6c)
(6d)
(6e)



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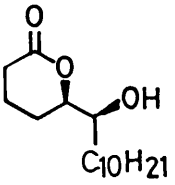


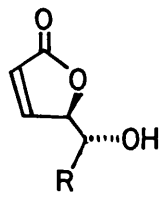
(8)

Footnote: The threo assignment is made in the cyclopentenone series on the basis of a staggered carbon chain backbone, where the two substituent groups have anti relationship. In the lactone series threo assignment is made by reference to threose, following the sugar conventions.

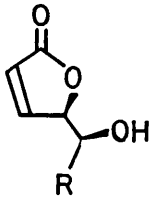
The lithium enolate of (1) (LDA,THF,-78°C) reacted with a range of aldehydes, giving threo (syn) and erythro (anti) adducts (5a)-(5e) and (6a)-(6e) in yields ranging from 70% to 85% with marked preference for the threo diastereomer (from 70:30 to 95:5, increasing with steric bulk of R.).[3] No 4-substitution was observed. Similar yields, but reversed diastereoselectivity, resulted from the zirconium enolates (LDA,$ZrCp_2Cl_2$), as observed for acyclic systems.[4]

Generally improved stereoselectivity was observed for Lewis acid catalyzed reactions of the trimethylsilyloxy diene (2).[5] A range of Lewis acids and solvents were explored and, optimally, $TiCl_4$/THF gave > 90% threo preference with, for example, 2-phenylethanal and 2-methylpropanal, although at the expense of total yield (50%).[2] This stereoselectivity is in accord with postulated transition states for silyl enolates,[6] with R 'exo' to the silyloxycyclopentadiene. [Note that no reaction could be induced by $Eu(fod)_3$ or $Pr(fod)_3$, in contrast to reactions of (4) which will be described] The threo preference was established by n.m.r. (δ CHOH 3.7,J=8Hz for threo; δ CHOH 4.2,J=2Hz for erythro)[7] and confirmed by reduction of (5a) and (6a) to known cyclopentanones.[7,8] Reversal of diastereoselectivity resulted when t-butylammonium fluoride was used to liberate the anion, giving typically a 20: 80 threo/erythro mixture.[9]

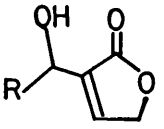
When (5e) and (6e) were catalytically reduced, and the resultant cyclopentanones subjected to Baeyer-Villiger reaction, the 6-hydroxyalkyl lactones (7) and (8) were isolated in good yields, the latter being related to a known mosquito attractant pheremone.[10] A facile route to such δ-lactones is thus apparent.



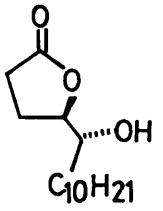
(9a) R = Me
(9b) R = Et
(9c) R = ^{i}Pr
(9d) R = $PhCH_2$
(9e) R = $C_{10}H_{21}$



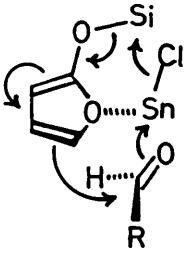
(10a)
(10b)
(10c)
(10d)
(10e)



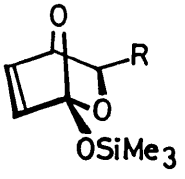
(11)



(12)



(13)



(14)

Interesting comparisons emerged from the corresponding chemistry of 2-(5H)furanone (3) and the derived silyloxydiene (4).[11] Again, these systems have received surprisingly little attention in synthesis,[12] and, in particular regioselectivity and diastereoselectivity have not systematically been explored.

The lithium enolate of (3) (LDA,THF,-78°) reacted with aldehydes to give a mixture of the γ-adducts (9a)-(9e) and (10a)-(10e), together with α-adducts (11), typically in a 1:1:6 ratio. Thus, no significant selectivity was achieved. However, silyloxyfuran (4) reacted with aldehydes in the presence of an extensive range of Lewis acids, the optimal conditions ($SnCl_4$,THF,-78°) affording threo/erythro ratios of 88:12. (In this series, threo is R,R/S,S). It should be noted that fluoride-initiated aldol reactions, although switching the selectivity, did not adequately discriminate between the diastereomers.) Initial assignments came from n.m.r. analysis of coupling constants, and lanthanide-induced shifts. More direct assignment was made by synthesizing a known precursor of the pheremone dispalure.[13] Thus, reactions of (4) with undecanal, and chromatographic separation of the major isomer (threo) gave racemic (9e) which was reduced (H_2,Pd-C) to give 5-hydroxyalkyl γ-lactone (12), spectroscopically identical to the dispalure intermediate. A general route to such γ-lactones, complementing that for the homologous δ-lactones described above, is thus exemplified.

Mechanistically, two explanations are possible for the threo selectivity. Firstly, a novel tricyclic chelate (13) may be invoked. In a concerted process the aldehyde is delivered to the 5-position, with R exo to give the threo products (9). This contrasts with the reaction of (2) in which the methylene group cannot thus be involved. A second mechanism recognises the fact that silyloxybutadienes, catalysed by lanthanides, give Diels Alder adducts.[14] Thus (4) could, via exo adduct (14), lead to threo products (9). Intermediate (14) could not be detected by direct n.m.r. monitoring of the reaction leading to (9a) and (10a), but this does not preclude the route. Interestingly, however, under the Danishefsky conditions[14] [$Eu(fod)_3$,0.5 mol%,$CHCl_3$,RT] no Diels Alder adduct was observed, but a change in regioselectivity of the aldol reaction occurred and good yields of α-adduct (11) were obtained, possibly in consequence of an alternative transition state leading to 2-(3H) furanone adducts and thence (11). Similar regioselectivity was observed for $Pr(fod)_3$.

In summary, 5-lithiocyclopentenone and trimethylsilyloxycyclopentadiene/$TiCl_4$ give predominantly threo 5-hydroxyalkylcyclopent-2-enone aldol adducts although reversal of diastereoselectivity can be achieved from the zirconium enolates or by fluoride-mediated reaction of the silyl enolate. In comparison, 2-trimethylsilyloxyfuran/$SnCl_4$ gives threo 5-hydroxyalkyl 2-(5H)furanones which are the γ-aldol adducts. These products are convertible, respectively, into threo 6-hydroxyalkyl δ-lactones (8) and threo 5-hydroxyalkyl γ-lactones (12).

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2. Yield refers to total diastereomers in the reaction as analysed by g.l.c., using internal standard. Isolated yield (medium pressure column chromatography) gave, typically, 30-50% of total separated diastereomers.

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5. Conveniently prepared from cyclopentenone (LDA,TMSCl,-78°), c.f. earlier Retro Diels Alder route; R. Bloch, Tetrahedron Letters, 1979, 3945.

6. See, for example, T. Mukaiyama, K. Banno and K. Narasaka, J.Amer.Chem.Soc., 1974, 96, 7503; T.H. Chan, T. Aida, P.W.K. Lau, V. Gorys and D.N. Harpp, Tetrahedron Letters, 1979, 4029.

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