STEREOSELECTIVE STUDIES
IN
THE BAYLIS-HILLMAN REACTION

(PART A)

by

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B.Sc. (Honours) Natal

A thesis submitted in partial fulfilment
of the requirements for the degree of

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DECLARATION

I hereby certify that this research is the result of my own investigation, which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed: _____

T. MANICKUM

I hereby certify that this statement is correct.

Signed: _____

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SUPERVISOR

Department of Chemistry
University of Natal
Pietermaritzburg
November 1992

This thesis is divided into *two* **PARTS:**

PART A: The thesis, excluding n.m.r.spectra.

PART B: N.m.r. spectra, which are *bound separately*.

TO JOANNE AND BYRON,
FOR THEIR SUFFERING.

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SUMMARY

In its simplest form, the Baylis-Hillman reaction involves addition of the ambident vinyl carbanion (nucleophile), generated by presence of a tertiary amine catalyst (i) to aldehydes (electrophile), to afford β-hydroxycarbonyl compounds, i.e., an aldol-type addition reaction.

The present investigation focussed on 1,2-*acyclic* diastereoselectivity in the above-mentioned reaction, *via* non-chelation controlled addition (absence of metal additives solvent, etc.) of the activated vinyl systems (ii) (*achiral* nucleophiles), to a series of protected chiral (and racemic) α-hydroxy and α-amino aldehydes (iii), with a view to assessment of some of the factors which contribute to control of the diastereofacial selectivity. The aldehydes were reasonably readily accessible from the chiral "pool" of α-hydroxy and α-amino acids.

Reaction rates were generally slow, and consequently it was noted that a considerable degree of racemisation of homochiral aldehydes had occurred under the basic (tertiary amine) conditions, in addition to their observed racemisation (acid-catalysed) during purification by flash chromatography.

During the course of this study, a novel method was developed for the determination of diastereomeric ratios during the course of this study, viz., use of trichloroacetylisocyanate (TAI) (iv), which should be considered as a convenient first course of action for such determinations.

With the α-alkoxy/methyl aldehydes, the sense of the diastereoselectivity was, in most instances, *anti*, as predicted, with modest to good diastereomeric ratios being observed (at best 81:19 *anti*:*syn*) even with relatively sterically demanding features present in the reactants.

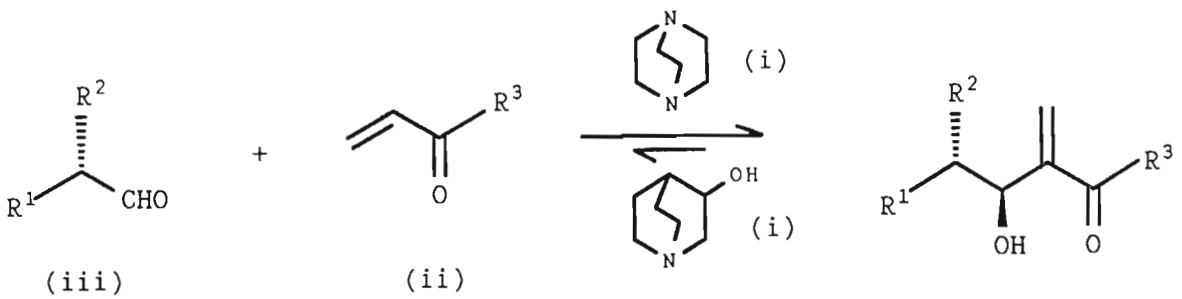
Asymmetric induction with the analogous *N*-protected amino aldehydes was observed to be dependent on the *type* of amino group protection, (i.e. manipulation of the *anti/syn* selectivity by selection of the amino group protection), in accordance with literature reports. This observed reversal of stereoselectivity thus extends the usefulness of the methodology. Similar degrees of induction (at best 87:13 *anti:syn*) were again observed.

Use of the TAI reagent (iv) was then extended to the assignment of *stereosubstructure* of the derived aldol-type derivatives (*anti/syn*) in addition to the use of the more established n.m.r.-based literature procedures.

The observed diastereoselectivities could, in most cases, be rationalised by the general "Felkin-Anh" (Felkin model and Anh-Eisenstein proposals) (v) and Cram "cyclic" (vi) models for 1,2-asymmetric induction. However, it was noted that steric effects as well as σ^* orbital energies are both important in determining the large "anti" group for application of the former model.

The synthetic utility of the derived multifunctional acrylates (vii) was further extended by their subsequent conversion to the biologically important α-methylene-γ- butyrolactones (viii).

The preliminary results from the double diastereoselection studies (which combined the 1,5-induction of chiral acrylates with the 1,2-induction) indicated that the *chosen* chiral acrylates (ix) and the alkoxy aldehyde (x) are not suitable candidates for achievement of the goals (high induction) of double asymmetric induction (double diastereo-selection/stereodifferentiation/) in *this* reaction.



(iii) (ii)

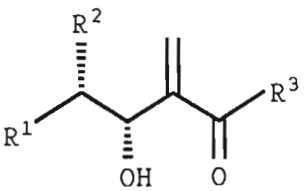
ANTI

R^1 = alkyl, aryl.

R^2 = alkyl, *O*-alkyl,
O-alkoxyalkyl,
H*N*(alkyl), *N*(alkyl)$_2$.

R^3 = OMe, Me, O^{t}Bu.

+



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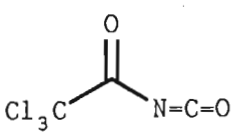

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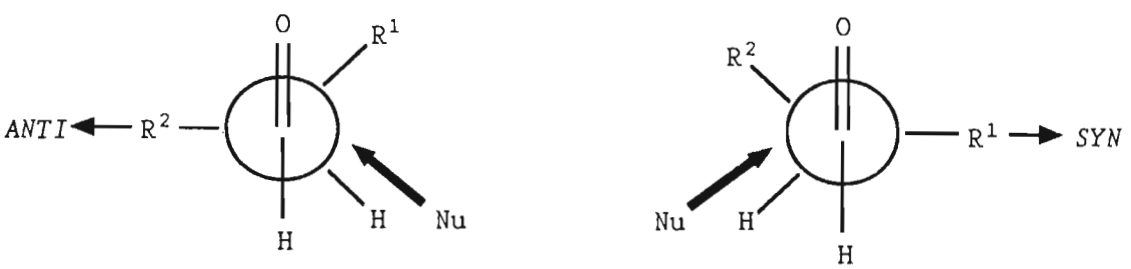

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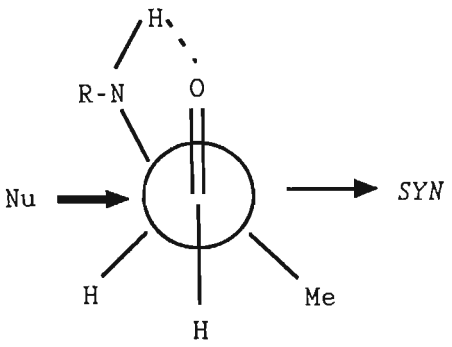

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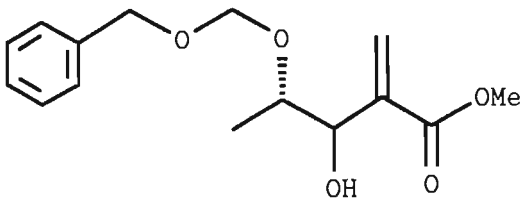

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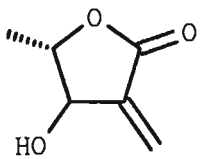

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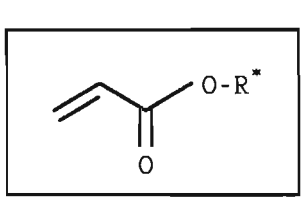
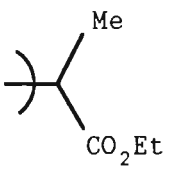
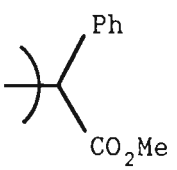
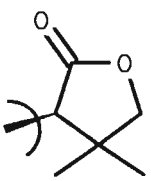
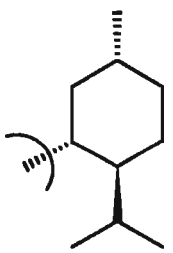
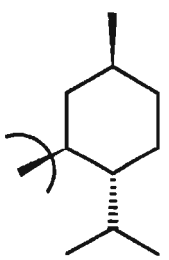


R* = 

R* = 

R* = 

R* = 

R* = 

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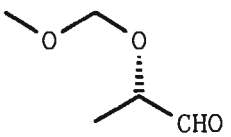


(x)

ABBREVIATIONS

Å	ångström/s
Abs	absolute
Ac	acetyl
atm	atmospheres
^{t}Boc	*tert*-butyloxycarbonyl
(^{t}Boc)$_2$O	di-*tert*-butyl dicarbonate
BOM	benzyloxymethoxy
b.p.	boiling point
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
Bz	benzyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionisation
COMPD.	compound
conc.	concentrated
CONFIGN.	configuration
d	day/s
d	doublet
D	DABCO
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[4.5.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets
d.e.	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DM	diastereomeric mixture
DMAP	4-dimethylamino pyridine
DMP	3,5-dimethyl pyrazole
DMSO	dimethyl sulfoxide
dt	doublet of triplets
dq	doublet of quartets
D.S.	diastereofacial selectivity

ed.	editor
e.e.	enantiomeric excess
e.g.	for example
EI	electron impact
Et	ethyl
etc.	*etcetara*
FG	functional group
FOD	tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)
GC/MS	gas chromatography/mass spectrometry
h	hour/s
hυ	light
HMPT	hexamethylphosphoric triamide
HOBT	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
i.e.	that is
J	coupling constant
L	large group/substituent
LDA	lithium diisopropylamide
Lit.	literature
m	multiplet
M	medium group/substituent
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
min.	minute/s
MOM	methoxymethyl
m.p.	melting point
Ms	mesyl
mth	month/s
MVK	methyl vinyl ketone
MW	molecular weight
n.m.r.	nuclear magnetic resonance
N.M.R	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhFl	phenyl fluorenyl
Pht	phthaloyl
PND	proton noise decoupled
^{i}Pr	*iso*-propyl
^{n}Pr	*n*-propyl
***p*-TsCl**	*para*-toluenesulfonyl chloride
***p*-TsOH**	*para*-toluenesulfonic acid
Py	pyridine
q	quartet
Q	(±)-3-quinuclidinol
R*	chiral moiety/fragment
re	*rectus*
r	molar ratio of acrylate to aldehyde
REDAL	sodium *bis*(2-methoxyethoxy)aluminium hydride
rt	room temperature
RXN	reaction
s	singlet
S	small group/substituent
si	*sinister*
t	triplet
TAC	trichloroacetyl carbamoyl
TAI	trichloroacetylisocyanate
TAMA	*N*-methylanilinium trifluoroacetate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
vic	vicinal
viz.	vizually
X_c	chiral moiety/fragment/auxiliary

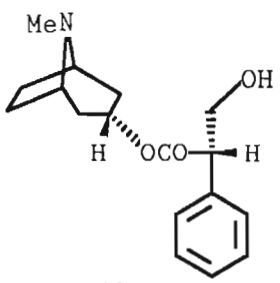
*	chiral/asymmetric centre/carbon
Δ	reflux
Δ	difference
Φ	dihedral angle
δ	chemical shift

CHAPTER 1

1. AN OVERVIEW OF ASYMMETRIC SYNTHESIS BY THE ALDOL REACTION AND RELATED METHODOLOGY.

1.1 ASYMMETRIC SYNTHESIS.

The synthesis of optically active organic compounds remains one of the most important challenges of contemporary synthetic chemistry. The influence of the shape of a molecule on its physiological action has been recognised for a long time.[1] For example, Cushney, in the early 1900's, demonstrated that one member of a pair of optical isomers could exhibit greater pharmacological activity than the racemate; (-)-Hyoscyamine (1) was approximately twice as potent as the racemate (Atropine) in its effect on pupil nerve endings.[2]



(1)

Crosby has clearly outlined the desirable reasons for producing optically pure materials in a recent review.[3] Manufacture of chemical products applied either for promotion of human health or to combat pests which otherwise adversely impact on the human food supply is now increasingly concerned with enantiomeric purity.

An increasing number of drugs, food additives and flavouring agents are being prepared by total synthesis, and, during recent years, has greatly contributed to progress in the controlled formation of new chiral centres.

Most syntheses reported in the literature to date have entailed an optical resolution performed at some stage of the synthetic sequence - preparatively a wasteful procedure. Moreover, resolution is usually tedious. It is economically and aesthetically appealing, however, to exclude unwanted optical isomers at the earliest possible stage. Strategically, this can be accomplished by two basic approaches:

(1) Synthesis of the target molecule can be designed so as to incorporate a chiral fragment of known absolute stereochemistry (chiron approach).[4]

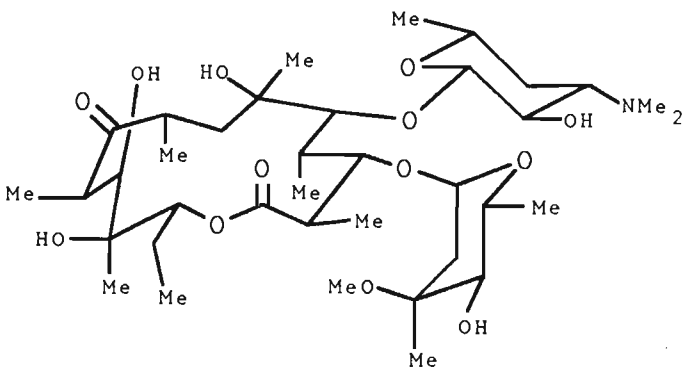
(2) Asymmetry in the target molecule may be induced under the influence of an external chiral auxiliary. Natures' chiral "pool"[4] (the amino acids, terpenes, α-hydroxy acids) furnish the source of chirality that can judiciously be used to ones advantage in diastereoselective processes.

The concept of asymmetric synthesis has been known for over eighty years. The term "asymmetric synthesis" was first used by E. Fischer[5] and defined by Marckwald.[6] Morrison and Mosher[7] proposed the following definition: "An asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products (enantiomeric or diastereomeric) are formed in unequal amounts." That is, an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result.

A rising proportion of syntheses[3] of homochiral materials include enzymatic transformations. This demonstrates the

increasing recognition of the contribution enzymes can make and willingness by the chemical community to employ them. However, considerable progress has been made by chemists to achieve comparable results without biochemical assistance. This is exemplified by the ever increasing number of recent results that demonstrate versatile, efficient, non-enzymatic transformations. The most serious obstacle continues to be a lack of complete understanding of all of the factors affecting asymmetric induction. The last two decades of approaches to asymmetric synthesis in organic chemistry has greatly contributed to progress in the directed introduction of various functionalities in the highly controlled formation of new centres of chirality. Complete harnessing of these processes still remains one of the cornerstone problems in the total synthesis of natural products.

The art of stereochemical control has become sophisticated, notably in the construction of rigid or conformationally well understood systems. The stereocontrolled elaboration of acyclic and other conformationally mobile compounds is a problem for which synthetic chemists have relatively few complete solutions. This area is becoming increasingly important as organic chemists focus their attention on the synthesis of, for example, macrolide and ionophore antibiotics, such as Erythromycin[8] (2).



(2)

The increase in this synthetic methodology is exemplified by the numerous reviews,[3,9] specialist conferences[3] and new journals[9a,10] dedicated to the topic that have appeared.

In an asymmetric reaction, substrate and reagent combine to form diastereomeric transition states. One of the two reactants must have a chiral centre to induce asymmetry at the reaction site. Most often, asymmetry is created upon conversion of trigonal carbon atoms to tetragonal ones at the site of functionality, involving groups such as carbonyl, enamine, enol, imine and olefin. Such asymmetry at carbon as well as induction by and creation of asymmetry at sulphur, is currently the major area of interest in the synthetic organic arena. The difference in free energy between the possible diastereomeric transition states so formed determines the ultimate excess of one antipode over the other.

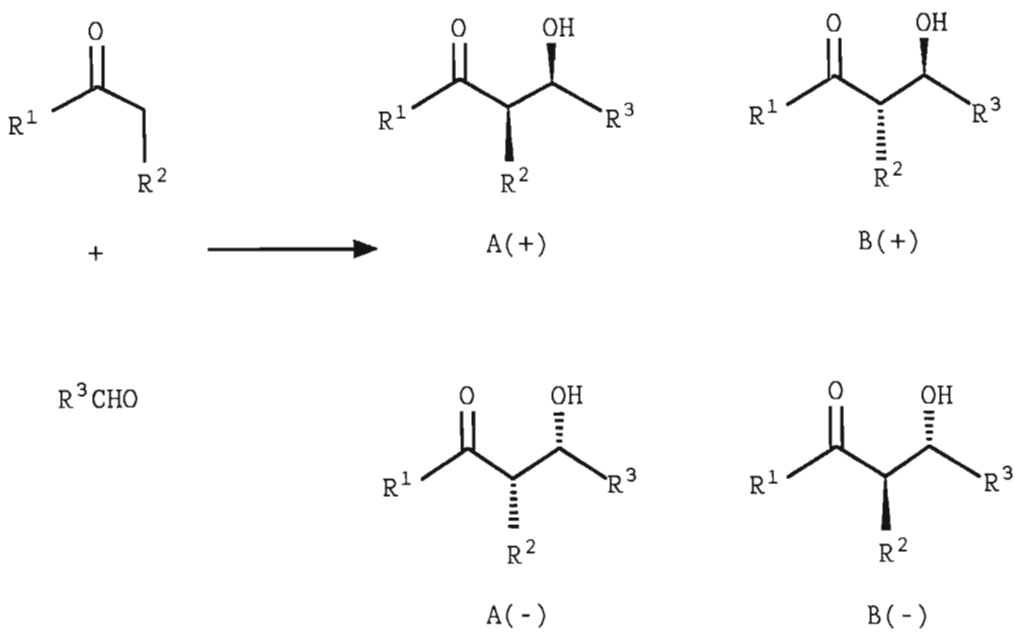
Amongst the important reaction types employed for the diastereo- and enantioselective modification of the creation of carbon-carbon bonds in organic molecules are the aldol,[11] nitro aldol[12] and Michael[13] addition reactions. Since the present investigation involves an aldol-type addition reaction, a brief review of stereoselection in the aldol reaction is relevant.

1.2 THE ALDOL REACTION.

The aldol condensation, one of the oldest organic reactions, continues its rebirth as a powerful method for the control of relative and absolute stereochemistry in the synthesis of conformationally flexible compounds. Although the aldol addition reaction was first reported in 1838,[14] there were only scattered observations pertaining to its stereo-

chemistry before 1970.[15]

In a general crossed aldol reaction, four possible stereoisomeric products result (EQUATION 1):



EQUATION 1.

Consequently, there are two stereochemical aspects associated with the reaction:

(1) Internal stereochemical control or DIASTEREOSELECTION, [A(±) vs B(±)].

(2) Absolute stereochemical control for a given diastereomer or ENANTIOSELECTION, [A(+) vs A(-) or B(+) vs B(-)].

1.2.1 SIMPLE DIASTEREOSELECTIVITY.

With respect to EQUATION 1, when both the enolate and the carbonyl compound are achiral (prochiral), a reaction that gives a surplus of one of these diastereomers is said to exhibit simple diastereoselection, where two new chiral centres are created.

1.2.2 DIASTEREOFACIAL SELECTIVITY.

With resident chirality in the aldehyde, the two carbonyl faces of the sp^2 prochiral centre of the molecule are now diastereotopic, rather than enantiotopic. That is, the chirality related to the differentiation is present in the substrate and the reaction can be classified as diastereoface-differentiating,[16] typically yielding diastereomers as products.

When an achiral reagent approaches the chiral substrate, the reagent will, in principle, exhibit a varying degree of preference for one face over the other. This degree of preference as reflected in the products is defined as diastereofacial selectivity.[17]

When asymmetric induction occurs at a newly generated chiral centre relative to a resident chiral centre in the molecule, the most easily established stereochemical relationships are those between adjacent carbons, that is, 1,2-stereoselection.

Relative asymmetric induction is more favoured when the chiral centres are closer to each other.[18] Reactions which establish 1,3; 1,4 and even 1,5-relationships are more difficult and rare, and thus, correspondingly, of greater

value.

1.2.3 STEREOCHEMICAL NOMENCLATURE.

With regard to diastereomer nomenclature, the issue has been addressed by both Heathcock *et al.*[19] and Masamune *et al.*[20] so that two conventions are now in common usage. Heathcock *et al.*[19] prefer the prefixes *erythro* and *threo*, used in the following sense, which are invariant of the nature of R^1 and R^3 (FIGURE 1):

when the backbone of the aldol is written in an extended (zig-zag) manner, with the α-alkyl substituent and the β-hydroxy substituent both extending toward or away from the viewer, that isomer is termed the *erythro* diastereomer [A(±)]; the other diastereomer, *threo* [B(±)].

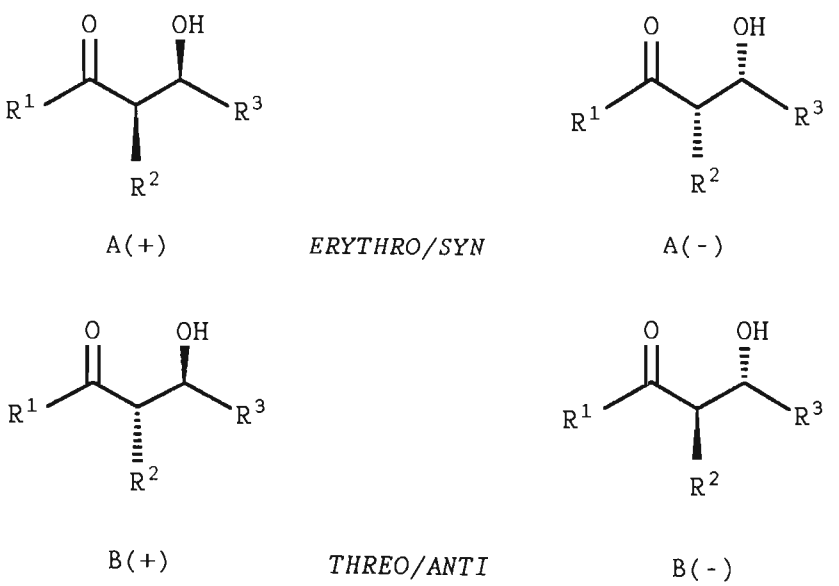


FIGURE 1.

In an analogous fashion, the stereochemical nomenclature of [A(±)] has been defined by Masamune *et al.*[20] as the *syn* diastereomer, and [B(±)] as the *anti* diastereomer, when the two substituents are on opposite sides of the main carbon chain (FIGURE 1).

The latter definition is adopted from this stage. In addition, the Cahn-Ingold-Prelog rules[21] (for assignment of absolute configurations (R/S), priority of ligands, *re-si* face, etc.) are applied.

1.2.4 STEREOCHEMICAL MODELS.

Great effort in the field of acyclic stereochemistry has been devoted to understanding and controlling relative asymmetric induction in nucleophilic additions to chiral carbonyl compounds.[7,22] The study originated with Fischer's[23] work on hydrogen cyanide addition to aldoses and led to efforts by Cram,[24,25,26] Prelog,[27] Conforth,[28] Karabatsos[29] and Felkin,[30] to provide consistent and useful models for the prediction of relative asymmetric induction. This development of theoretical treatments continues to the present.[31,32,33] The relationship between the selectivity of the addition of the nucleophilic reagent to the carbonyl group, the reagent structure and reaction conditions continues to be an object of extensive studies.

The specific conformations of carbonyl substrates, which were originally considered to explain α-asymmetric induction, are *briefly* illustrated below.

1.2.4.1. THE CRAM "OPEN-CHAIN" MODEL.

Cram proposed an "open-chain"[24] model, based on either a one- or two-conformer option, for simple alkyl-substituted carbonyl compounds where the carbonyl oxygen and the largest α-substituent adopt an *anti*-relationship for the addition. The one-conformer model is illustrated in FIGURE 2.

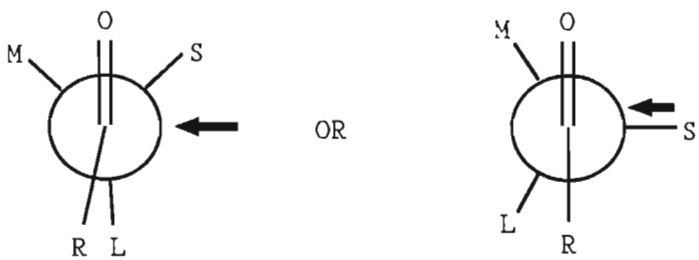


FIGURE 2.

1.2.4.2 CONFORTH'S DIPOLAR MODEL.

For halo derivatives, the carbon-halogen and carbonyl dipoles prefer an *anti* conformation (FIGURE 3).[28]

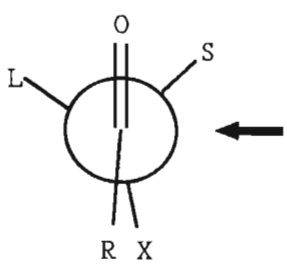


FIGURE 3.

1.2.4.3 THE CRAM "CYCLIC" MODEL.

For compounds containing an α-substituent capable of coordinating the cationic part of the reagent (nucleophile), for example, hydroxy, alkoxy and amino groups, this model[25,26] predicts that this substituent will be eclipsed with the carbonyl by formation of a chelate in the favoured conformation (FIGURE 4).

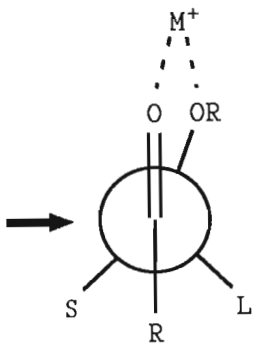


FIGURE 4.

In each case described above (FIGURES 2, 3 and 4), nucleophilic addition, as indicated by the arrow, occurs preferentially from the least encumbered side of the π-bond, that which contains the smallest substituent.

While the above models generally guide synthetic chemists in their predictions of the major isomer products, quantitative discrepancies between predicted and observed results, as substituents are systematically varied, has led more recently to alternative postulations. One of the more successful, alternative models is that of Felkin.[30]

1.2.4.4 THE FELKIN MODEL.

Here it is proposed[30] that the appropriate conformations to consider for the "open-chain" model are those in which the bond to the largest α-substituent is perpendicular to the carbonyl group. The carbonyl oxygen is considered to be less sterically demanding than the R-substituent, therefore favouring conformation A on the basis of the R↔S versus R↔M gauche interactions (FIGURE 5).

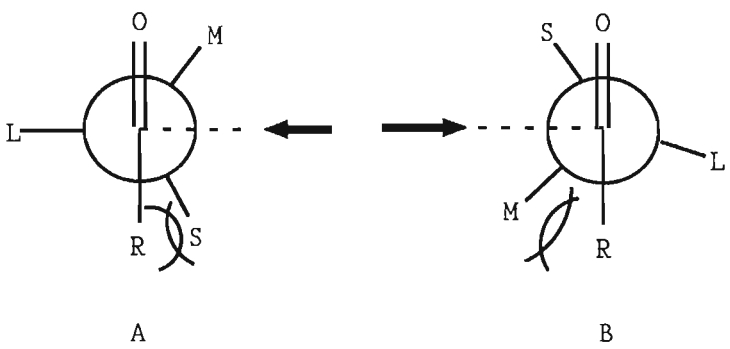


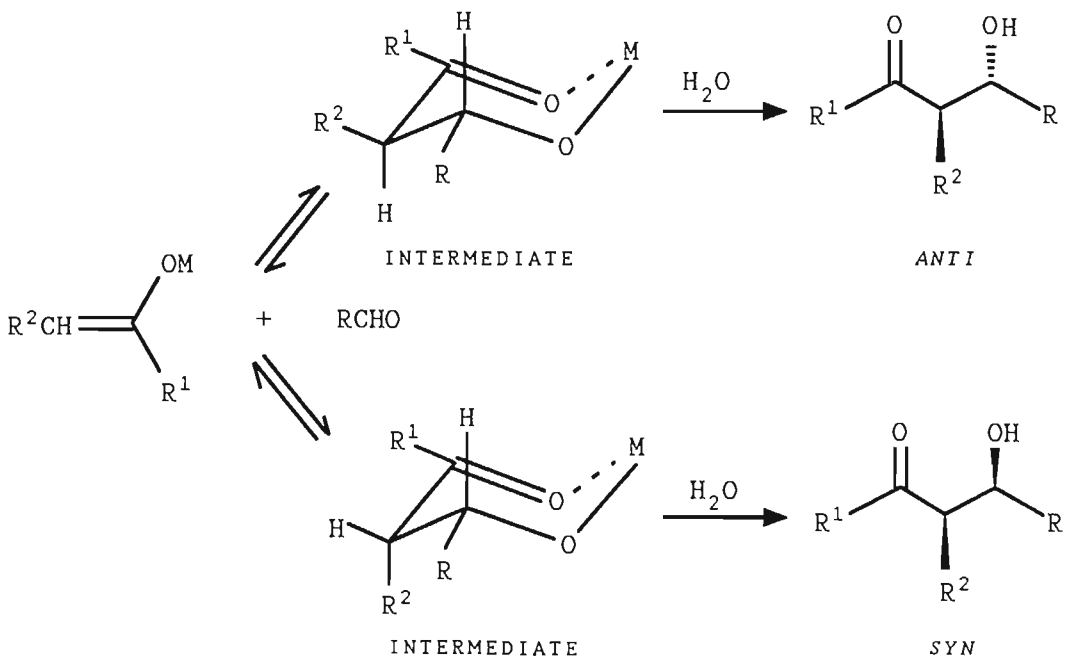
FIGURE 5.

1.2.5 DIASTEREOSELECTIVITY.

It has been well established that either kinetic or thermodynamic principles can be employed in the aldol reaction to define product stereochemistry.

1.2.5.1 THERMODYNAMICALLY CONTROLLED ALDOL DIASTEREOSELECTION.

When conditions are chosen such that the condensation process is rendered reversible, the more stable *anti* metal aldolate complex is usually the dominant diastereomer observed,[34] since the more stable chair-like conformer of the intermediate metal chelate has the maximum number of equatorial substituents (SCHEME 1).[11b]



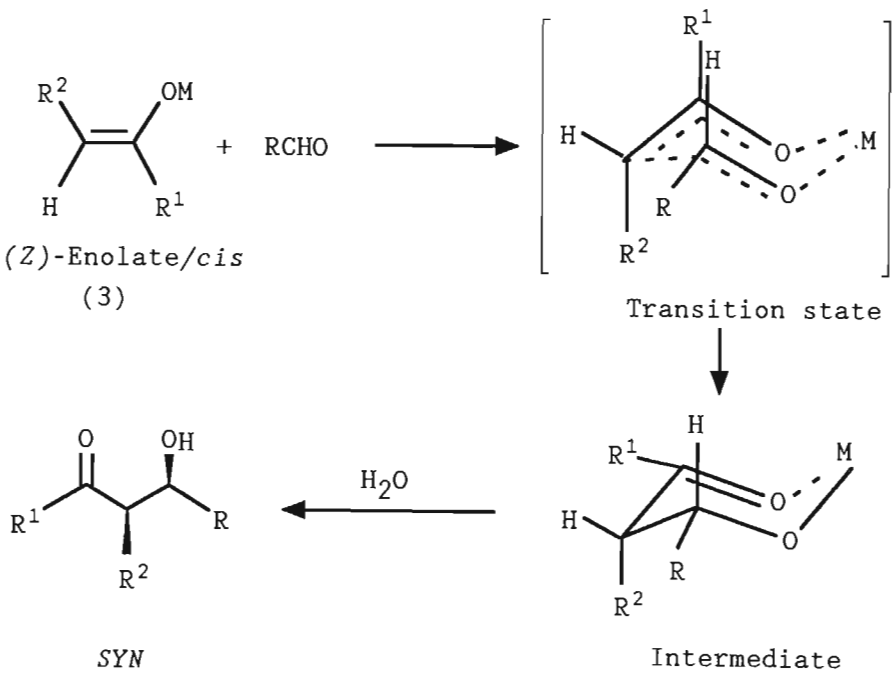
SCHEME 1.

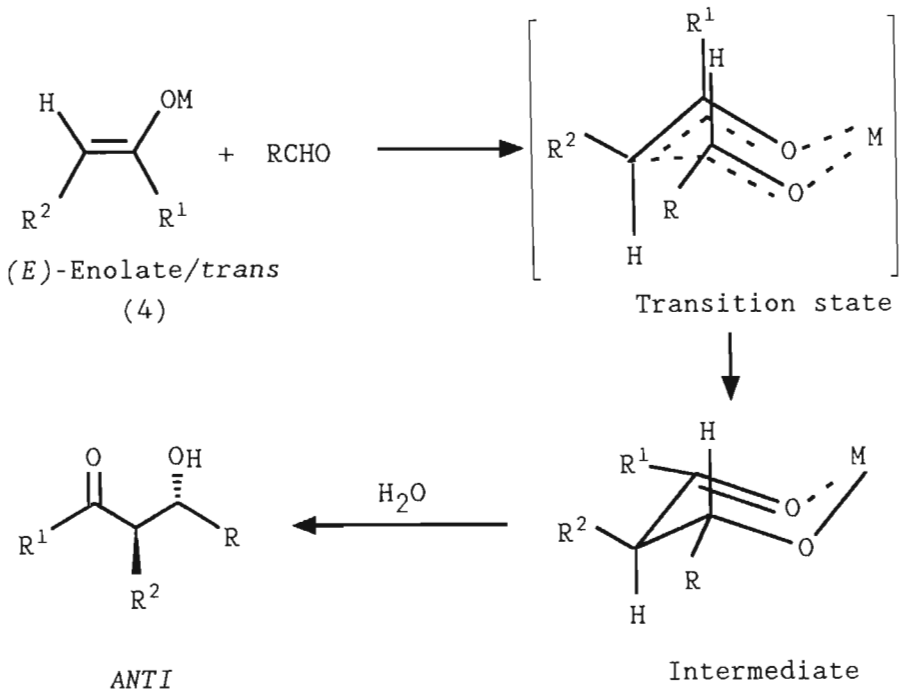
The rate and extent of *syn/anti* equilibration depends on the nature of the cation M and the carbonyl ligand R^1. Data suggest equilibration towards the *anti* isomer may be favoured by using better chelating metals, such as Zn.[19]

1.2.5.2 KINETICALLY CONTROLLED ALDOL DIASTEREOSELECTION.

The ideal of designing highly enantioselective aldol condensations demands that all aspects of bond formation be kinetically controlled. It is well known that kinetic aldol stereoselection is, to a great extent, defined by enolate geometry.[19,35] The terms *cis* and *trans* can be used to refer to the relative disposition of the α-substituent R^2 and the carbonyl oxygen.

Structure (3) (SCHEME 2) possessing a *cis*-stereochemical nomenclature relationship between the enolate ligand R^2 and the oxygen substituent (OM), has also been referred to as (*Z*)-enolate. Similarly, the *trans*-stereochemical relationship between R^2 and (OM), as in (4) (SCHEME 2), has been designated as the (*E*)-enolate.





SCHEME 2.

Investigations of enolate geometry in the aldol,[19,36] have resulted in the following generalisations:

(1) The (*E*) isomer is favoured under kinetic conditions by the use of co-ordinating counter cations,[37] non-bulky groups at R^1 and R^2 (SCHEME 2),[19] bulky bases[38] and non-polar solvents which favour an organised transition state.

(2) The (*Z*) isomer tends to be formed under thermodynamic conditions or under kinetic conditions with bulky R^1 and R^2 groups and the use of sterically small bases, non-complexing counter cations and a solvent which effectively solvates the cation.

Studies[39] related to the outline in SCHEME 2 (the pericyclic intermediate proposed by Zimmerman and Traxler[40]) reveal the following trends:

(1) (*Z*) [or (*E*)] enolates give preferentially *syn* (or

anti) aldols, except for some intramolecular reactions.

(2) (Z)-enolates are generally more selective than (E)-enolates.

(3) The steric demands of R^1 and R^2 dominate the degree of diastereoselectivity, whilst variation of R has little or no effect.

1.2.6 CHELATION VERSUS NON-CHELATION CONTROL.

In order to control stereoselectivity, two strategies have been developed :

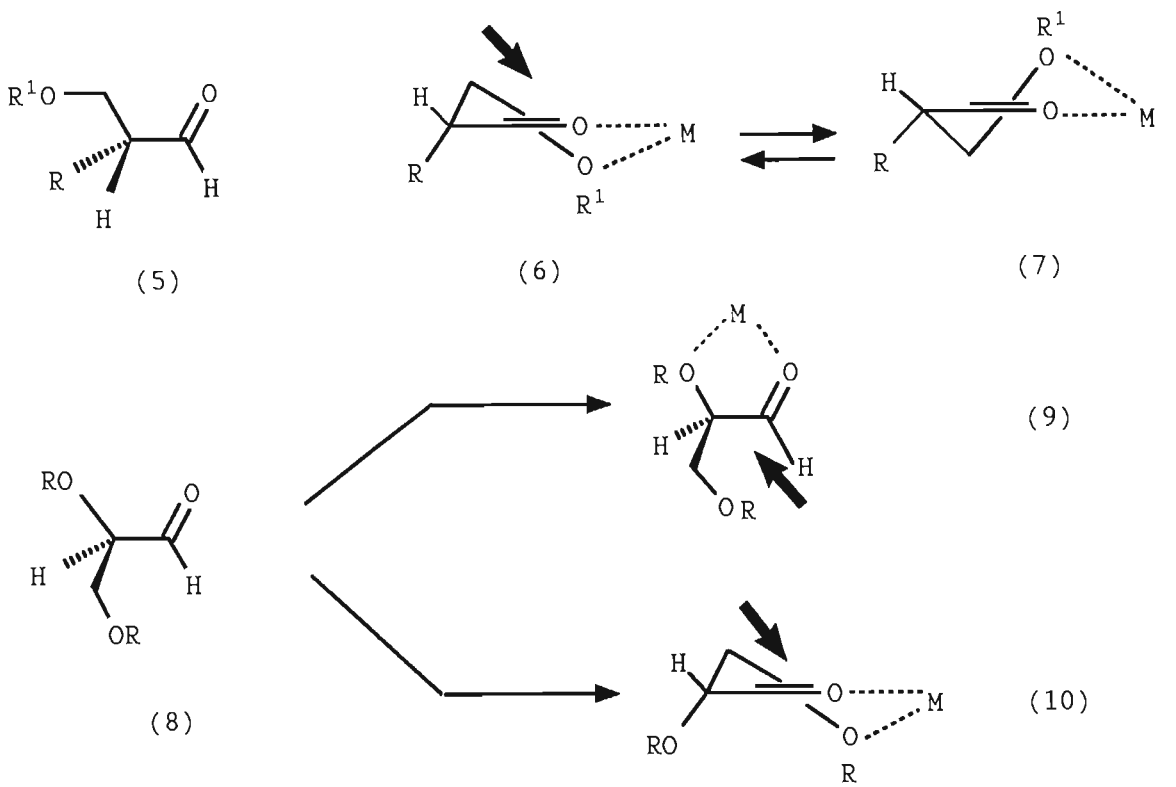
(1) Use of Lewis-acidic reagents to form intermediate chelates, which are attacked stereoselectively from the less hindered side (chelation control). Activation of an aldehyde (RCHO) is generally assumed to occur *anti* to the R-group, and chelation necessarily involves *syn* complexation.

(2) Use of reagents incapable of chelation, stereoselective attack being governed by electronic and/or steric factors, notably those defined by the Felkin-Anh[30-32] or Conforth[28] (dipolar) models (non-chelation control). Non-chelation-controlled reactions are a formidable task because there is no general way to reduce the number of degrees of freedom of non-complexed molecules.

Generally, the two methods lead to the opposite sense of diastereoselectivity [*syn* in (1) and *anti* in (2)]. It is possible to predict the stereochemical outcome by careful choice of organometallic reagents containing elements such as Li, Mg, B, Si, Sn, Cu, Zn or Ti. An excellent review by Reetz[41] outlines the concepts of chelation and non-chelation controlled reactions with chiral alkoxy carbonyl compounds.

The aldehyde (5) reacts with Lewis acids to give the che-

late (6), the arrow indicating the preferred direction of attack (SCHEME 3).[41]



SCHEME 3.

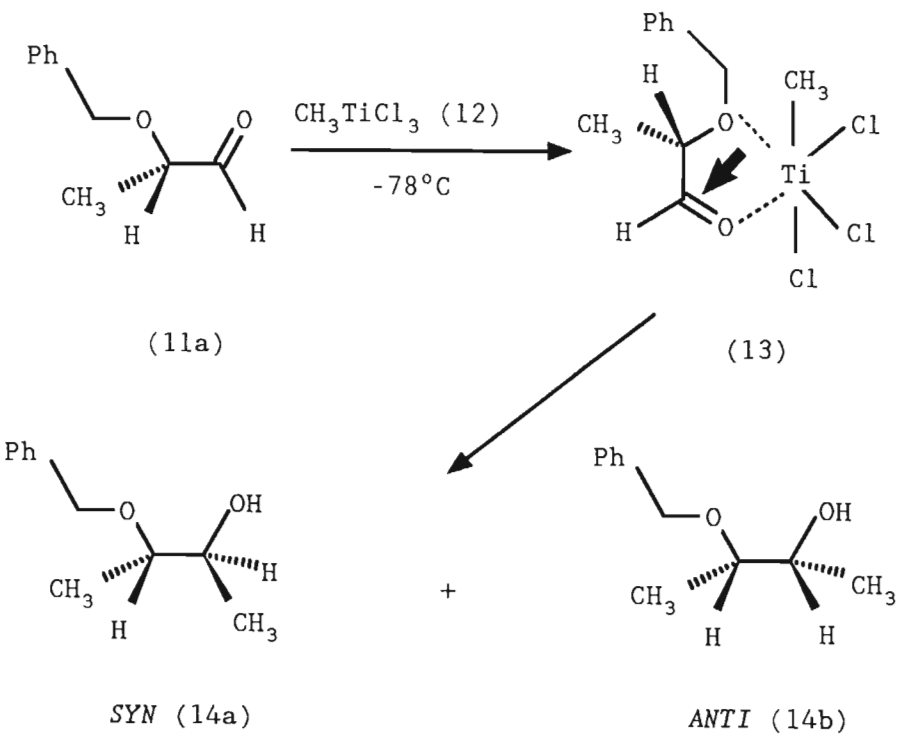
Instead of (6), the alternative half-chair conformation (7) may also be involved. With the dialkoxy aldehyde (8), α-co-ordination leads to (9) and β-coordination to (10), in which opposite diastereotopic faces of the carbonyl group are exposed.

Chelation in (10) is analogous to that in (6), but the diastereoselectivity might be expected to be enhanced because the non-complexed RO group facilitates an "Anh-effect".[41]

Generally, low temperatures are beneficial although the converse has been observed.[41]

In early studies devoted to the application of organotitanium reagents to organic synthesis, Reetz *et al.*[41] discovered that CH_3TiCl_3 (12) undergoes chemo- and stereoselective carbon-carbon bond forming reactions with carbonyl compounds.[41] Furthermore, (12) as well as $TiCl_4$, readily formed octahedral complexes with two donor molecules (e.g., diethyl ether, THF), or with bidentate ligand systems.[41] These observations set the stage for testing Lewis-acidic titanium reagents in chelation-controlled reactions of α-alkoxy carbonyl compounds.

Addition of (12) to the aldehyde (11a) led to (14a) and (14b) in the ratio 92:8, consistent with an intermediate of the type (13)[41] (EQUATION 2).

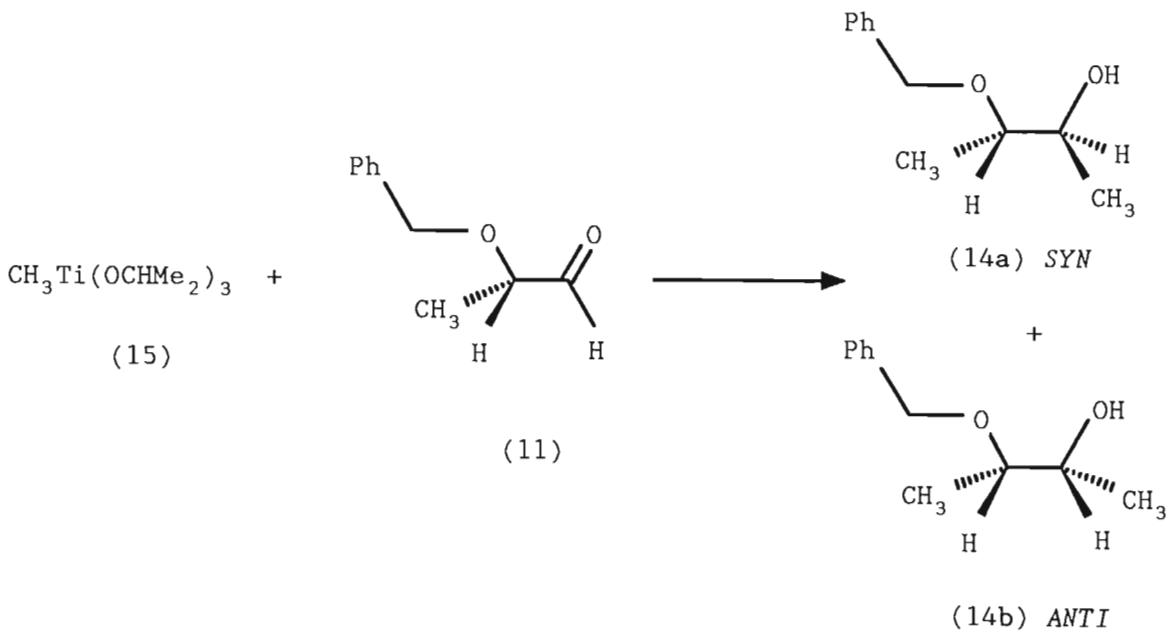


EQUATION 2.

$TiCl_4$ and $SnCl_4$ are similar in that both are capable of forming six-coordinate octahedral complexes.[41] For α-chelation, $SnCl_4$ is more efficient than $TiCl_4$.[41]

Silyl enol ethers are also excellent carbon nucleophiles for chelation-controlled aldol additions to α-alkoxy aldehydes.[41] Allyl and crotylstannanes add to α-alkoxy aldehydes in chelation-controlled processes mediated by Lewis acids such as $TiCl_4$, MgX_2 or ZnX_2.[41]

The Lewis acidity of alkyltitanium reagents decreases drastically in going from $RTiCl_3$ to $RTi(OR')_3$.[41] Thus, it was observed by Reetz *et al.*[41] that the complex $CH_3Ti(OCHMe_2)_3$ (15) reacted with (11) to afford preferentially the "Felkin-Anh" product (14b) (14a:14b = 8:92) (EQUATION 3). Thus, chelation or non-chelation control is possible in a predictable way by varying the ligands at titanium.



EQUATION 3.

Further examples of a variety of other nucleophiles (lithium acetylides,[42] activated butadienes,[43] lithium enolates of ethyl-1,3-dithiolane-2-carboxylate,[44] amino carbene complexes,[45] enes,[46] diethyl zinc,[47] etc.) have also been reported to proceed with good to excellent chelation control on addition to α-chiral, (and/or α-alkoxy) aldehydes.

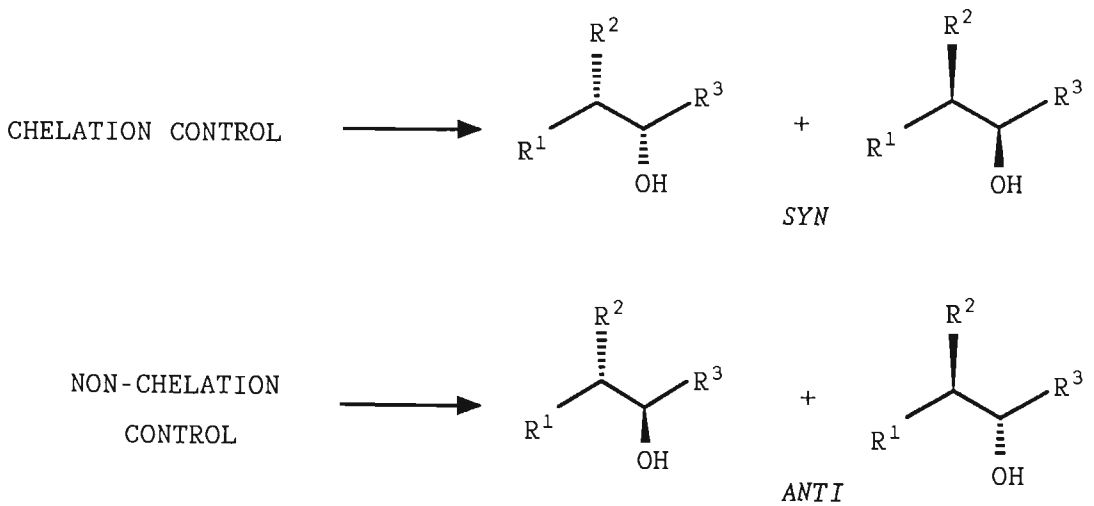
A more difficult task is the development of new and better ways to achieve non-chelation control.

In summary it is evident that both models (the Cram "cyclic" and the Felkin-Anh "open chain") assume different transition states leading to opposite diastereomers as major products.

In general, :

(1) The *syn* isomer is the major product in chelation-controlled reactions (Cram "cyclic" → "Cram" product) (SCHEME 4).

(2) The *anti* isomer is the major product in the absence of chelation (Felkin-Anh "open chain" → "non-Cram" product) (SCHEME 4).



SCHEME 4.

1.3 α-O, *N*-SUBSTITUTED CHIRAL ALDEHYDES.

Aldehydes are important building blocks in organic synthesis. In recent years, there has been a growing interest in chiral non-racemic aldehydes because of the development of new and effective methods for controlling stereochemistry of reactions, such as aldol addition.

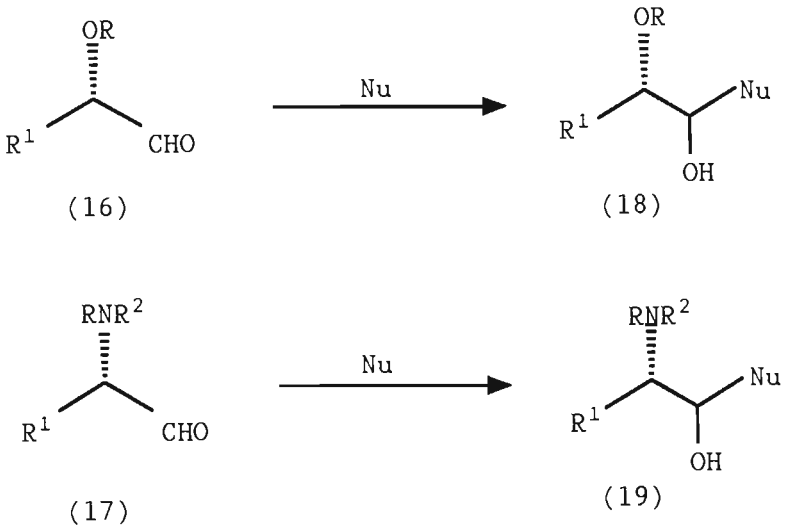
Protected α-hydroxy and α-amino aldehydes (16) and (17) (FIGURE 6) are of special interest, owing to their ready availability in both enantiomeric forms from natural sources (α-hydroxy acids and α-amino acids) and to their pronounced functional versatility.

(16) (17)

FIGURE 6.

One-carbon homologation of chiral α-hydroxy aldehydes should have numerous synthetic applications, particularly for the synthesis of the less common (L)-sugars and of deoxysugars and amino sugars.[49]

Stereoselective additions of carbon nucleophiles to protected α-chiral hydroxy or amino aldehydes affords the corresponding 1,2-diol (18), or the β-amino alcohol moiety (19) (SCHEME 5).

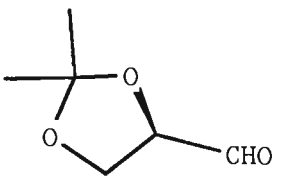


(16) (18)

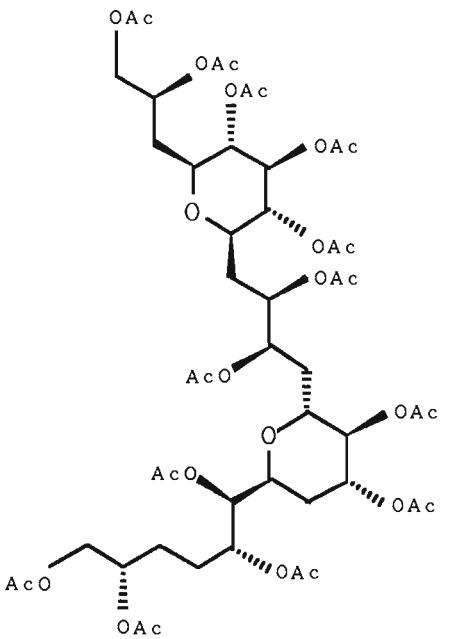
(17) (19)

SCHEME 5.

Utility of these building blocks for the construction of complex molecules, and their essential features as bio-synthetic intermediates has been amply demonstrated,[48,50] e.g., application of (R)-2,3-O-isopropylideneglyceraldehyde (20) to the synthesis[50] of (21), a fragment of Polytoxin, a natural product (FIGURE 7).



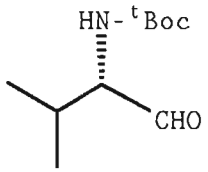
(20)



(21)

FIGURE 7.

The chiral β-amino alcohols and their derivatives are key features in many organic compounds, viz., natural products, [for example, (L)-Statine[48] (23), present in protease inhibitors, which has been synthesised from the chiral *N*-protected α-amino aldehyde (22) (FIGURE 8)], medicinal compounds, peptide and peptide analogs.



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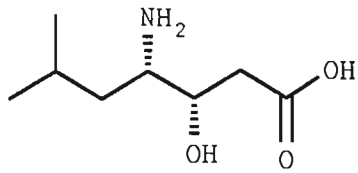
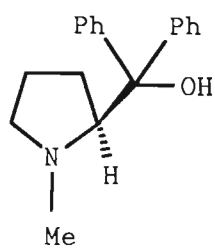


(23)

FIGURE 8.

These amino alcohols have also been used as chiral auxiliaries, for example (24),[51] in catalytic enantioselective reactions.



(24)

Efficient methods for their synthesis are thus desirable. Consequently, extensive work has been carried out,[48-52] (variation of reaction conditions, protecting groups, nature

of the nucleophile, etc.), in order to maximise the degree of diastereoselectivity obtained.

Several excellent reviews on the application of protected (chiral) α-hydroxy[11a,49,50,53] and *N*-protected α-amino aldehydes[48,52] in stereocontrolled organic synthesis have thus appeared. A number of syntheses of natural products, starting from *N*-protected α-amino aldehydes, involve the aldol reaction as the key step. Unfortunately, these aldol additions,[48] in contrast to the substantial levels of diastereoselectivity obtained with the chiral α-alkoxy carbonyl compounds, are characterised by rather low diastereoselectivity.

1.3.1 DOUBLE DIASTEREOSELECTION.

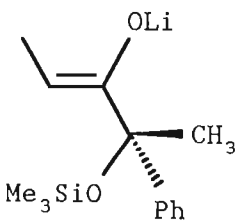
As is evident, even from the previous synopsis, a staggering number of examples address the problem of stereoselectivity in a wide variety of chemical transformations. These include (single) asymmetric synthesis,[53] i.e., where reaction of an achiral reactant with a second optically pure (homochiral) reactant produces a mixture of optically active products, e.g., reaction of an achiral enolate with a chiral aldehyde (or carbonyl compound).

When both the enolate and the aldehyde are chiral, the inherent diastereoface preferences of the two reactants may reinforce one another (consonant double stereodifferentiation), or they may oppose one another (dissonant double stereodifferentiation).[54,55] In principle, 1,2 (or even 1,3; 1,4; etc.) diastereoselectivity can be enhanced by the use of "double stereodifferentiation."[16] This technique, as applied to the aldol condensation, has been illustrated by Heathcock *et al.*[55] Double stereodifferentiation experiments

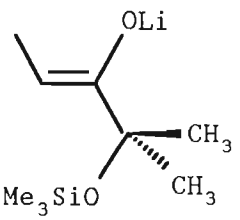
and its applications in aldol condensations toward the synthesis of lactones, macrolides, polyether antibiotics, etc., have been reported by several groups.[56]

Recently, a thorough review, qualitatively relating the stereoselectivities in single to that of the corresponding double asymmetric reactions, was published by Masamune *et al.*,[57] who outlined a new strategy for stereochemical control in organic synthesis. In summarising the large body of experimental data obtained both in his laboratories and those of other workers, Masamune proposed the *rule of multiplicativity*[57] which states that the degree of asymmetric induction obtained in a double asymmetric synthesis is approximated by ($a \times b$) for a *matched* pair and ($a \div b$) for a *mismatched* pair, where a and b are the D.S. (diastereofacial selectivity) for each of the chiral reactants involved.

The following set of aldol reactions[57] illustrates the definitions of *matched* and *mismatched* pairs :



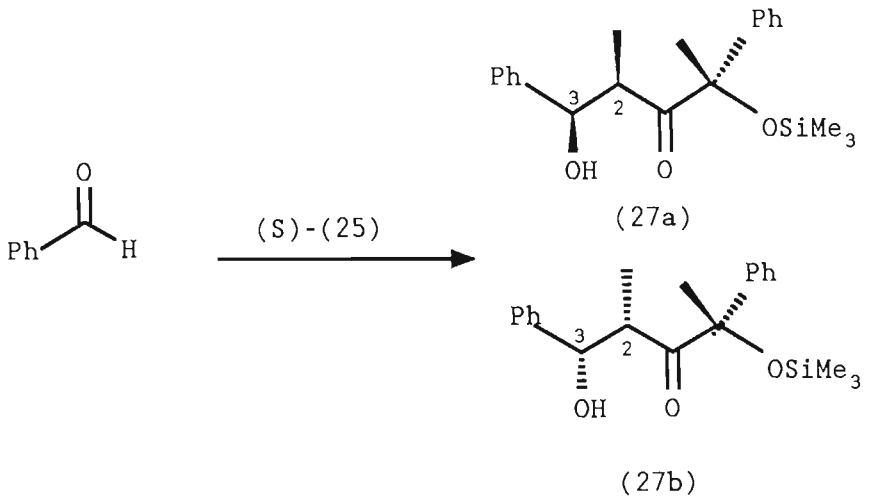
(S)-(25)



(26)

FIGURE 9.

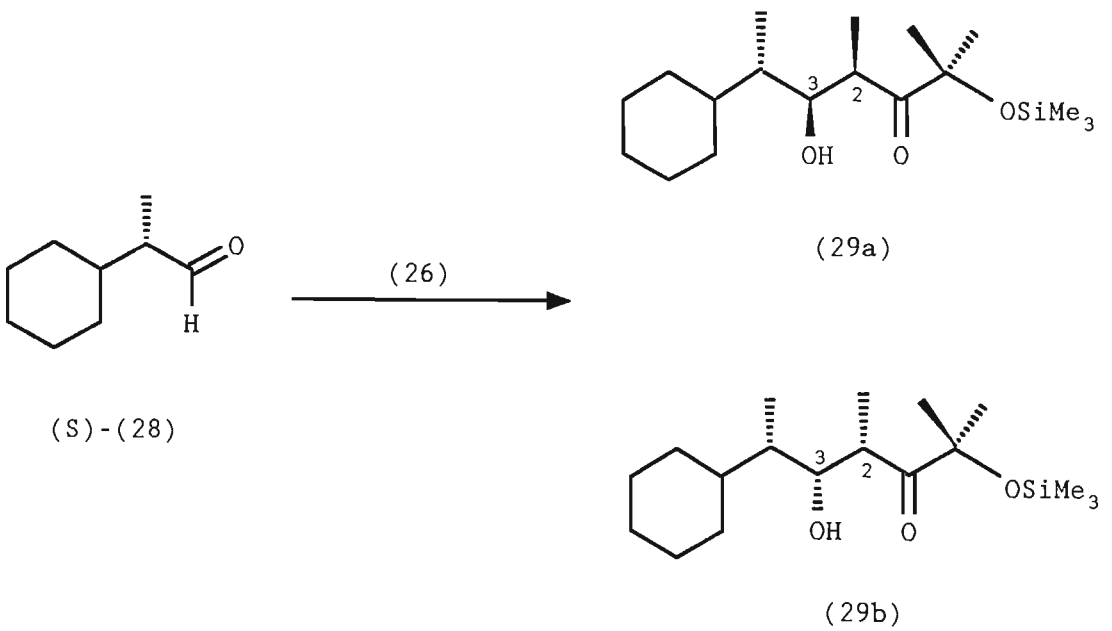
The chiral lithium enolate (S)-(25) reacts with achiral benzaldehyde to provide the diastereomeric aldol products (27a) and (27b) in a 3.5:1 ratio, which represents the D.S. of (25) (EQUATION 4).



EQUATION 4.

The two substituents at C-2 and C-3 are *syn*-related but their absolute configurations are different; both β in (27a) and both α in (27b).

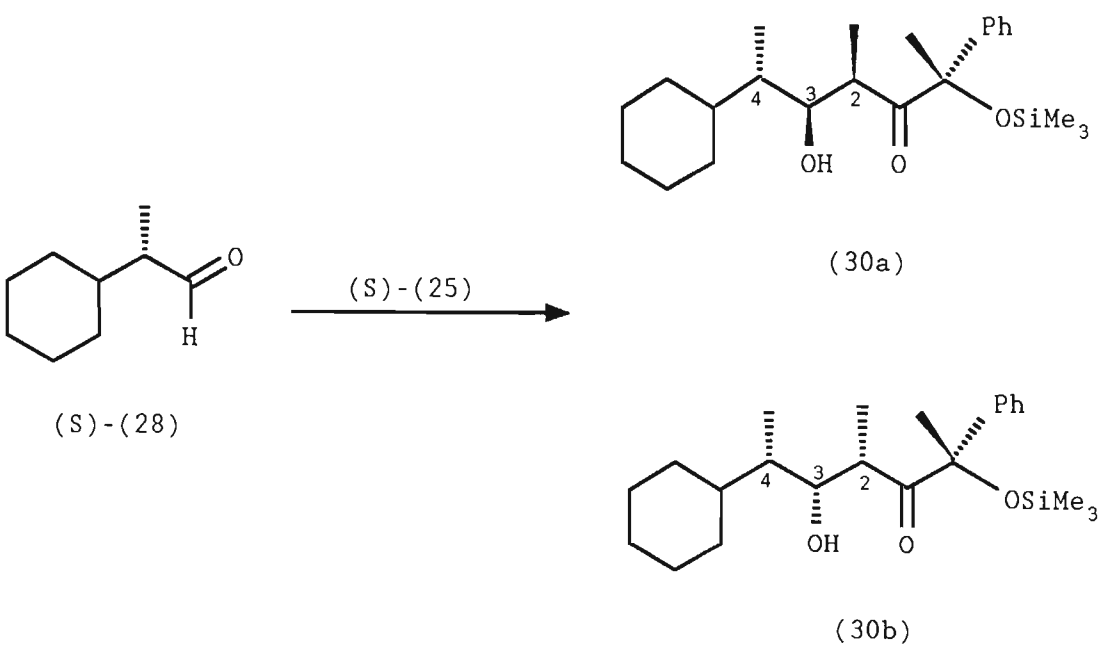
Likewise, using the achiral lithium enolate (26) (FIGURE 9), the D.S. of the aldehyde (S)-(28) is determined to be 2.7:1, the ratio of the two products (29a) and (29b) (EQUATION 5).



EQUATION 5.

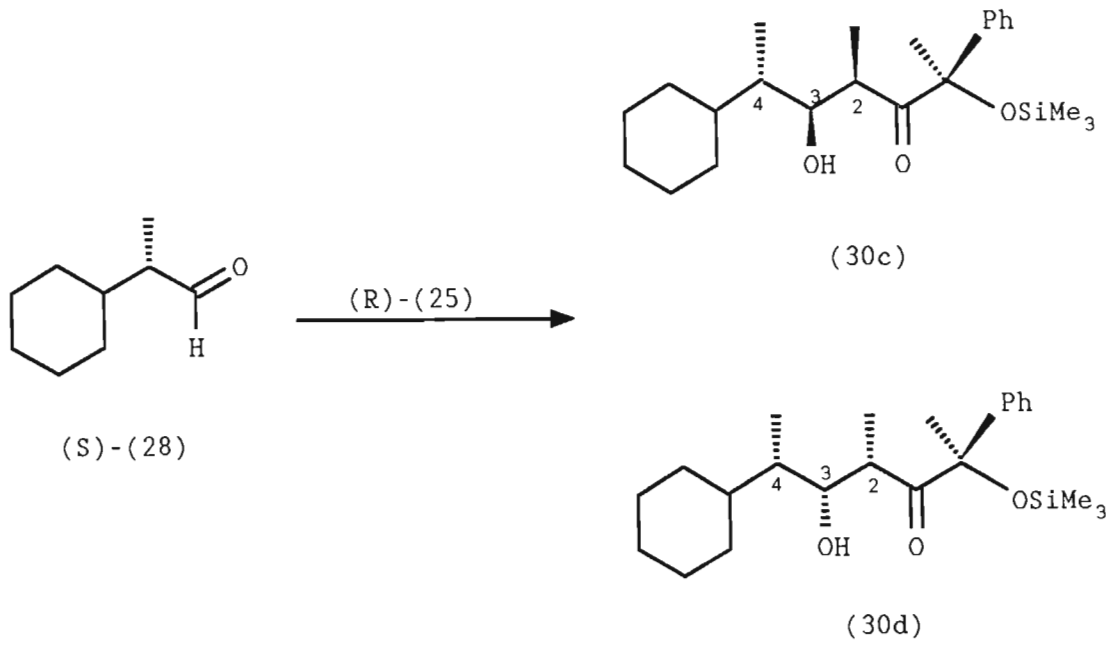
Inspection of the absolute configurations of the C-3 hydroxyl groups in (27a) and (29a), both of which are the predominant products of the above two reactions, immediately suggests that (S)-(25) and (S)-(28) constitute a *matched* pair.

In fact reaction of this pair leads to enhancement of stereoselection (8:1), providing the major product (30a) which incorporates the C-3 hydroxy group in a β-configuration and with an *anti*-relationship to the 4-methyl group (EQUATION 6).



EQUATION 6.

The corresponding *mismatched* pair of (S)-(28) and (R)-(25) reacts with inferior stereoselection (1:1.5) as predicted (EQUATION 7).



EQUATION 7.

Further aldol studies[57] have demonstrated the *approximate*, qualitative characteristic of the multiplicative rule. This arises in part from the variable nature of the D.S. values assigned to each of the reactants, which critically depend on the *chiral and achiral analogues chosen* for the comparison reactions.

Chiral enolate reagents that exhibit a greater than 100:1 diastereofacial selectivity in the aldol reaction are rare at present, and documented examples of such double asymmetric induction using such reagents are even more scarce.

The ideal criteria[57] set for the chiral enolate reagent are that it exhibits greater than 95% *syn* or *anti* selection and ≥100:1 diastereofacial selectivity.

Two distinct features of natural product synthesis based on the above synthetic strategy should be emphasized:

(1) Synthesis of the target molecule in optically active form, since any substrates to be used in double asymmetric synthesis are homochiral.
(2) The process of retrosynthetic analysis for many stereochemically complex molecules and the execution of the synthetic plan are substantially simplified.

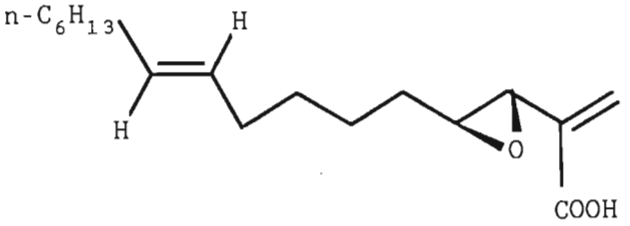
A critical evaluation of the above strategy, which uses homochiral reagents for stereochemical control (reagent control), in comparison with the traditional strategy, which uses chiral substrates for the same purpose, has been made by Masamune *et al.*,[57] using several examples of macrolide synthesis. The power and distinct advantages of this approach of double asymmetric induction is self-evident.

1.4 ACRYLATE AND RELATED SYSTEMS.

1.4.1 GENERAL SYNTHESIS.

1.4.1.1 NATURAL OCCURRENCE.

Yu and Helquist[58] have highlighted the fact that the acrylate unit features prominently in a large number of naturally occurring substances that possess biological activity, for example, Conocandin[59] (31), a fungistatic antibiotic isolated from *Hormocus conorum*, the germacrolide[59] (32), Euparin and Tremetone derivatives[60] (33) and the α-methylene-γ-butyrolactones containing the unusual β-hydroxy substituent, such as Tulipalin B (34)[62] (FIGURE 10).



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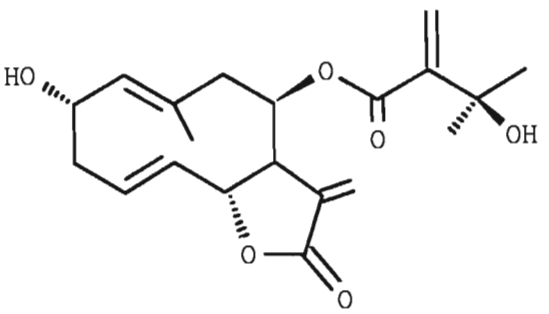

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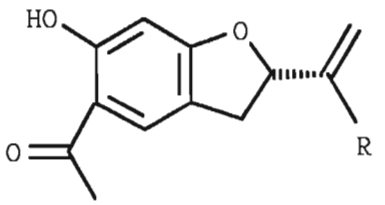
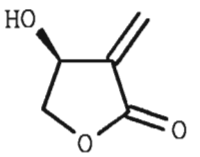


R=CH_3, CHO, CH_2OH, CH_2OAc

(33)

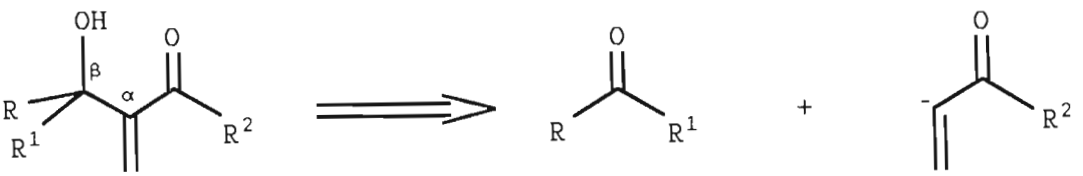


(34)

FIGURE 10.

1.4.1.2 METHODS.

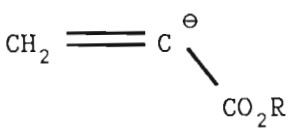
Retrosynthetic analysis for the synthesis of β-hydroxyalkyl acrylates and related groups (35), is an aldol-type condensation of a synthetic equivalent of a vinyl carbonyl α-anion (37) and a carbonyl compound (36), as the most direct approach (SCHEME 6).



(35) (36) (37)

SCHEME 6.

The acrylate moiety can be introduced in the desired system by a direct procedure involving either:
(1) A formal vinyl carbanion (38), or



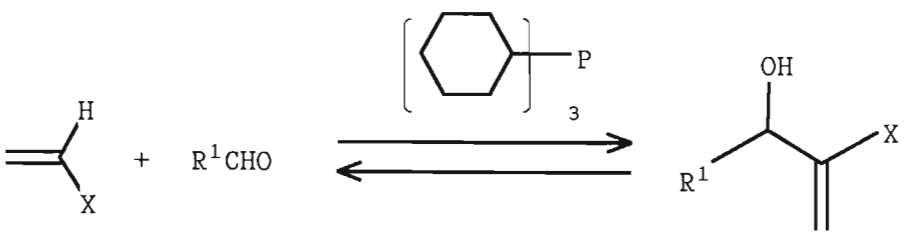
(38)

(2) By making use of a so-called masked acrylate or acrylate anion equivalent.

The former direct formation of vinyl carbanions (38), from monosubstituted acrylates by strong bases, such as LDA, is

only of limited use due to facile anionic polymerisation of the acrylic esters.[63] As a result, several synthetic equivalents of the acrylate anion (38) have been developed.[64]

Morita *et al.*[65] reported, for the first time, the isolation of 2-hydroxyalkyl derivatives of acrylate and related systems (39), in the presence of a catalytic amount of tricyclohexylphosphine (EQUATION 8).



(39)

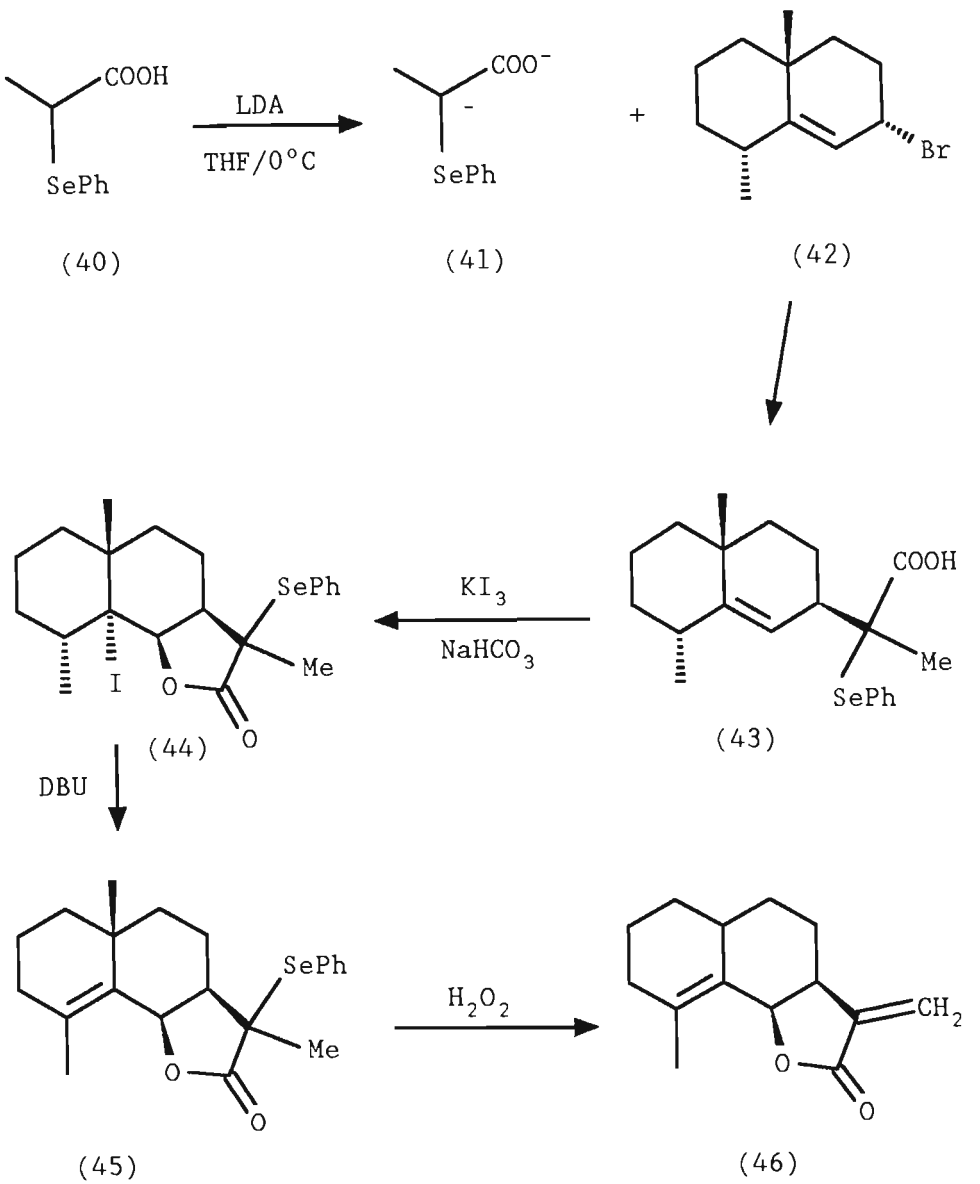
X= CO_2R, CN

R^1= alkyl, phenyl, substituted phenyl

EQUATION 8.

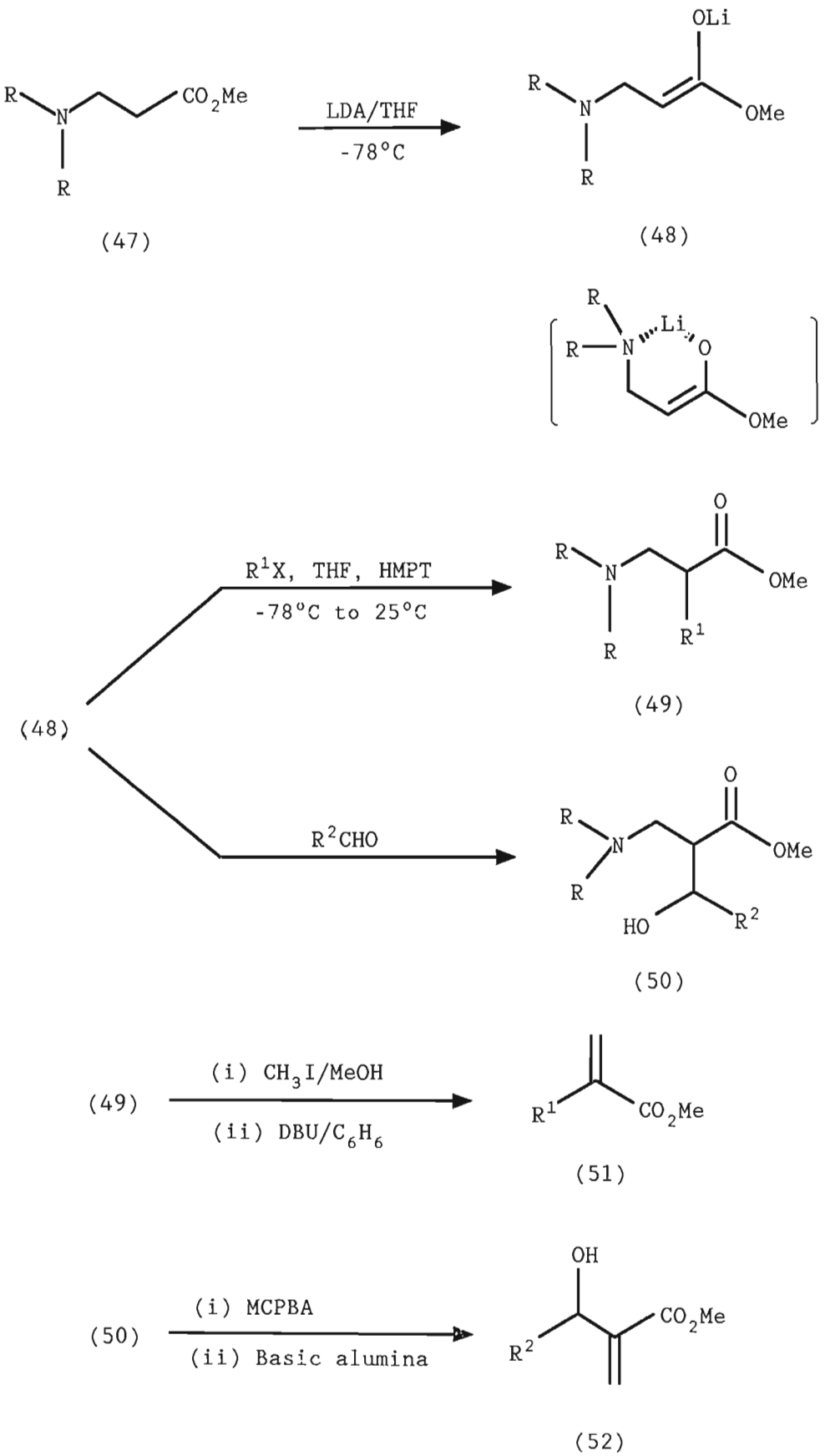
However, conversion of the α,β-unsaturated reactant was poor (23%).

The technique of masked acrylates has been used with considerable success, as illustrated by Petragnani and Ferraz,[66] who utilised a selenium-containing reagent (40) as an acrylate anion equivalent for the synthesis of an α-methylene lactone (46) (SCHEME 7).



SCHEME 7.

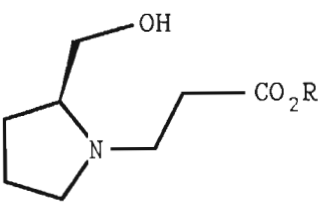
An alternative approach is the utilization of an acrylate synthon of general structure Z-CH_2CH_2COOR, in which the Z-group, after appropriate modification, finally serves as the leaving group in an elimination reaction that unmasks the acrylate system. This approach was adopted by Yu and Helquist,[58] who developed the lithium salt (48) as a synthetic equivalent of the acrylate anion (SCHEME 8).


R
N
R
CO2Me
LDA/THF
-78°C
OLi
OMe
(47)
(48)
Li
O
R1X, THF, HMPT
-78°C to 25°C
(49)
R2CHO
HO
R2
(50)
(i) CH3I/MeOH
(ii) DBU/C6H6
(51)
(i) MCPBA
(ii) Basic alumina
OH
(52)

SCHEME 8.

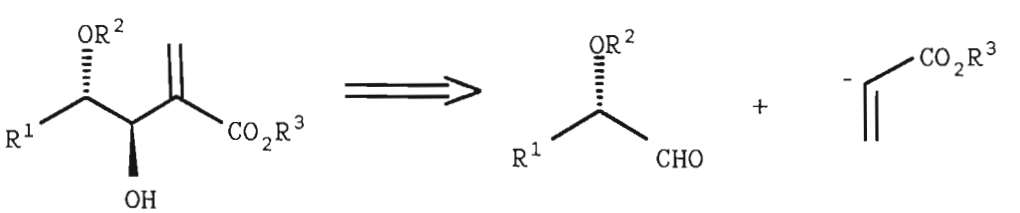
The enolate (48), obtained by treatment of the free ester (47) with LDA, is subsequently reacted with electrophiles (alkylating agents,[58] aldehydes). Deprotection of the addition products (49)[58] and (50), which are actually masked acrylates, affords the free α-substituted acrylates (51) and (52) (SCHEME 8).

Drewes and co-workers[67] have extended this system further by use of a chiral Z-group (53) which made possible the synthesis of chiral α-hydroxyalkyl acrylates.



(53)

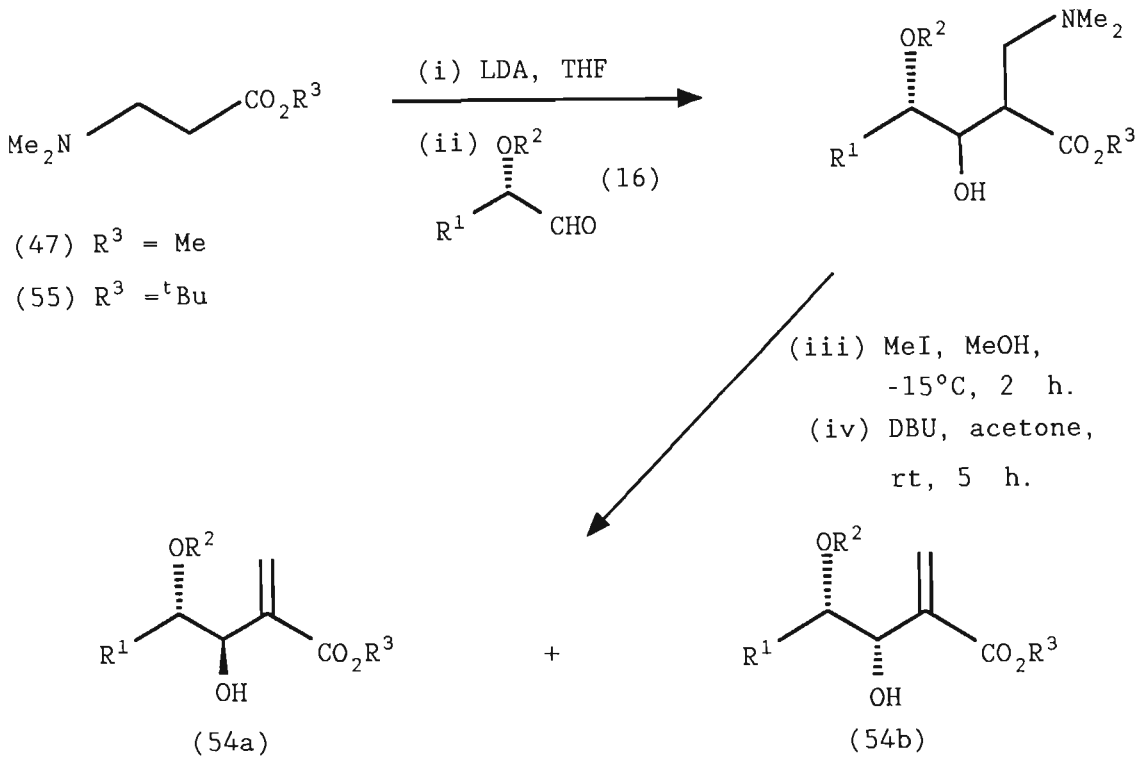
The above methodology (Yu/Helquist)[58] was adapted for α-chiral aldehydes by Scolastico and co-workers.[68] In developing a method for the stereoselective synthesis of *anti* esters of general formula (54a), an aldol-type condensation between a chiral α-alkoxy aldehyde (16) and a synthetic equivalent of acrylate α-anion was proposed[68] (SCHEME 9).



(54a) (16)

SCHEME 9.

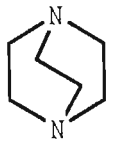
They achieved unprecedented high stereoselectivity in the aldol-type condensation of β-(dimethylamino)propionates (47) and (55) (up to 24:1 *anti*:*syn*) with a series of α-chiral (and racemic), α-alkoxy aldehydes (16) (SCHEME 10) in their studies directed toward the total synthesis of Conocandin (31).



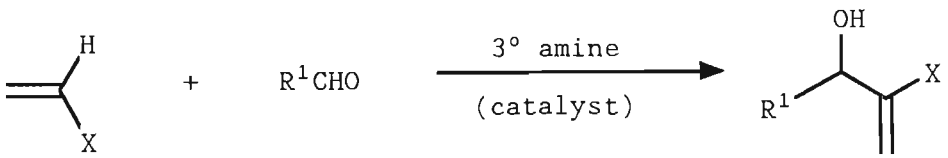
SCHEME 10.

1.4.2 THE BAYLIS-HILLMAN REACTION.

This reaction (EQUATION 9) has its origin in the patent granted to Baylis and Hillman in 1972,[69] who reported the successful coupling reaction of α,β-unsaturated systems (esters, nitriles, amides, ketones) with various aldehydes, catalysed by sterically hindered cyclic tertiary amines, such as DABCO (56).



(56)



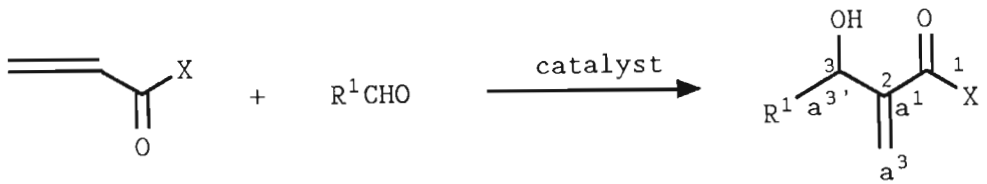
X = CO_2R, COR, CN.

EQUATION 9.

The above reaction leads to formation of a vinyl carbanion through the intermediacy of the catalyst. Reaction conditions are extremely mild and very few problems and unwanted side reactions are experienced. Several studies, including catalysts, mechanism, rate enhancement, effects of temperature and pressure and stereoselective synthesis have been carried out on the Baylis-Hillman reaction. In an excellent review, Drewes and Roos[70] drew attention to the synthetic potential of this tertiary amine-catalysed reaction, which continues to attract attention.

1.4.2.1 VERSATILITY OF PRODUCTS.

Stereoselectively prepared β-hydroxyalkyl acrylates (or β-hydroxyenones) (57) (EQUATION 10), have a wide use in natural product synthesis.



X = OR, R

(57)

EQUATION 10.

They offer a wide variety of functionality as a^1, a^3 and $a^{3'}$ components, using the Seebach nomenclature.[71] Consequently, extensive applications of these valuable intermediates, especially with respect to reactions at C-1 to C-3, have been made. These include conjugate addition with rearrangement,[70] conjugate addition,[70] addition of amines,[70] hydrogenation,[70] α-methylene-γ-lactones,[70] α-methylene-γ-lactams,[72] diene esters,[73] epoxidation[74] and novel tetrahydrofuran derivatives.[75]

1.4.2.1.1 THE α-METHYLENE-γ-BUTYROLACTONES.

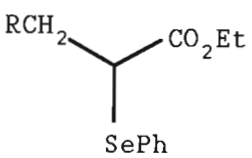
The most commonly occurring derivatives are the well known α-methylene-γ-butyro- and, to a lesser extent, the α-methylene-δ-valerolactones. An extensive amount of research has been carried out on them due to their cytotoxic and anti-tumour activities.

Although the presence of the α-methylene-γ-butyrolactone unit is essential for biological activity, other factors which may enhance these properties include the presence of hydroxyl groups in stereochemically strategic positions and

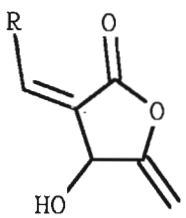
the presence of various conjugated ester side chains.[76] Although their exact role is not clear, the presence of hydroxyl groups adjacent to the α-methylene group is a common feature among a number of sesquiterpene lactones showing *in vivo* antitumour activity.[76]

There are a large number of methods available for the synthesis of α-methylene-γ-butyrolactones.[77] Synthesis of such analogues, utilising the built-in functionality of carbohydrates, has been reported.[76]

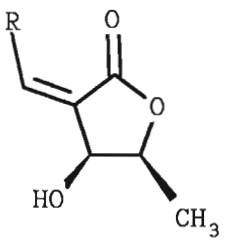
The use of α-phenylselenyl esters (58) as acrylate α-anion equivalents, provided a very direct and convenient synthesis[78] of α-alkylidene-β-hydroxy-γ-methylene- (59) and γ-methyl butyrolactones (60) (FIGURE 11).



(58)



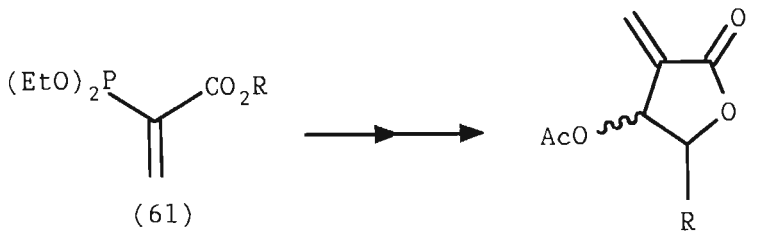
(59)



(60)

FIGURE 11.

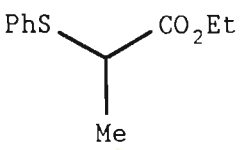
The first general method for the preparation of the β-hydroxy analogues of α-methylene-γ-butyrolactones (62) was reported by Benezra and Corbet,[79] who utilised the α-methylene phosphonate derivative (61) as an acrylate anion equivalent (EQUATION 11).



(61) (62)

EQUATION 11.

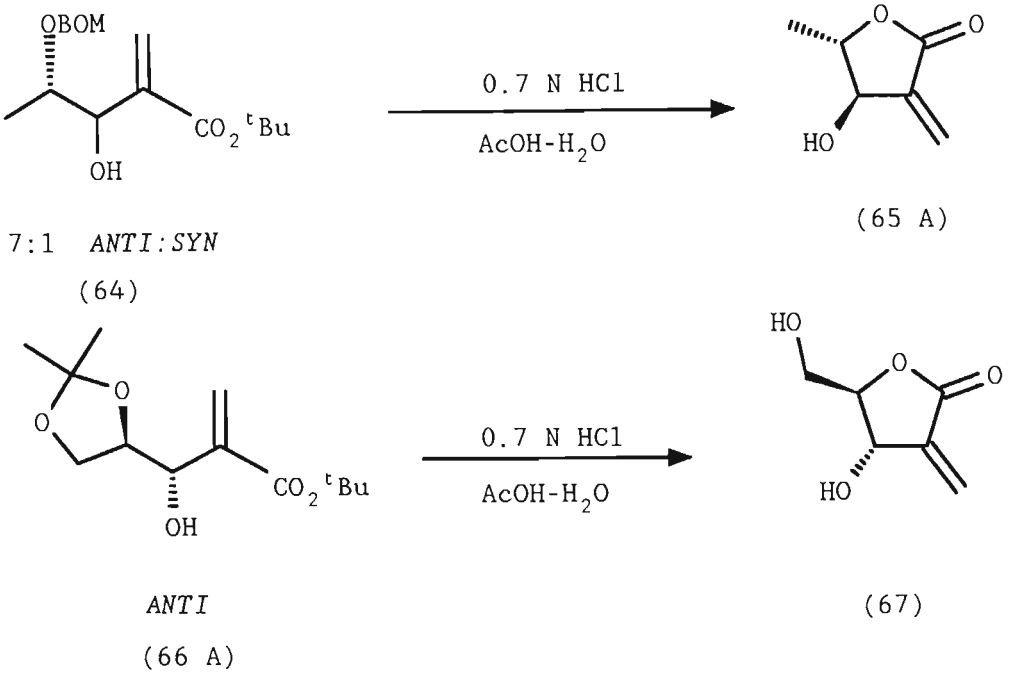
In another method of preparation, Barbier and Benezra[80a] utilised the acrylic ester equivalent, ethyl-2-(phenylthio)-propionate (63), to achieve the same goal.



(63)

The above procedure was subsequently successfully modified[80b] to obtain chiral β-hydroxy acrylates.

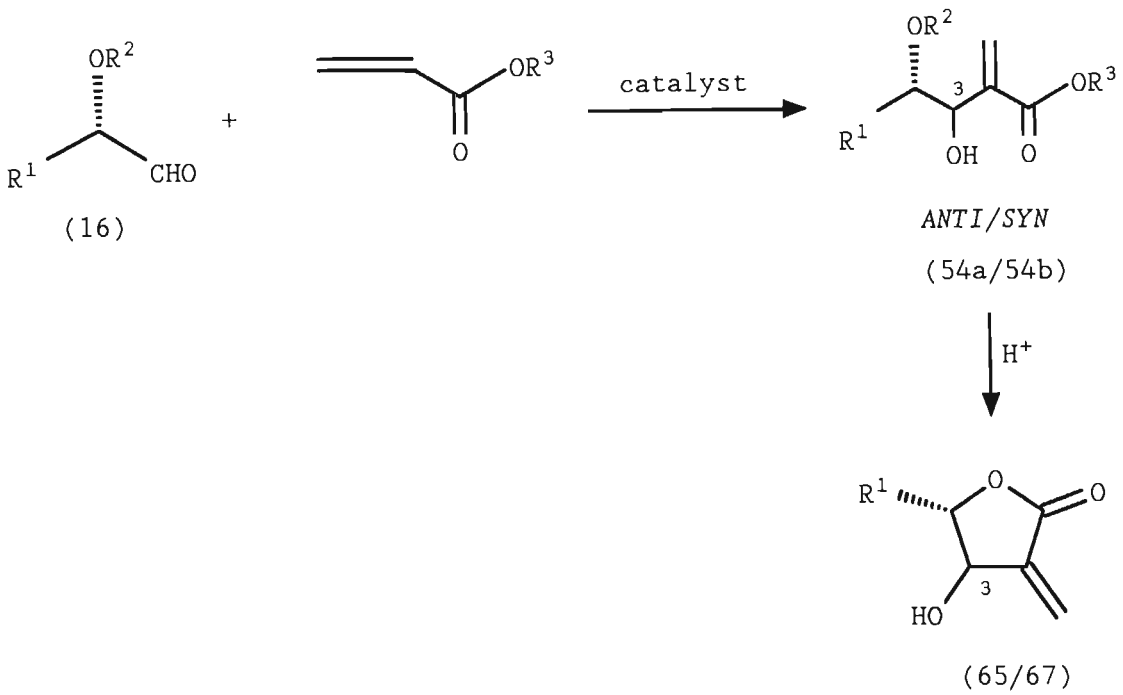
Scolastico and co-workers[81] reported the first general method for synthesis of the α-methylene-β-hydroxy-γ-butyrolactones (65 A) and (67) in optically pure form, without starting from sugar precursors (SCHEME 11).



SCHEME 11.

The α-methylene-β-hydroxy-γ-alkoxy esters (64) and (66 A), derived by use of the Yu/Helquist method, were easily lactonised, by acidic treatment, to the corresponding α-methylene-β-hydroxy-γ-butyrolactones (65 A) and (67) (SCHEME 11).

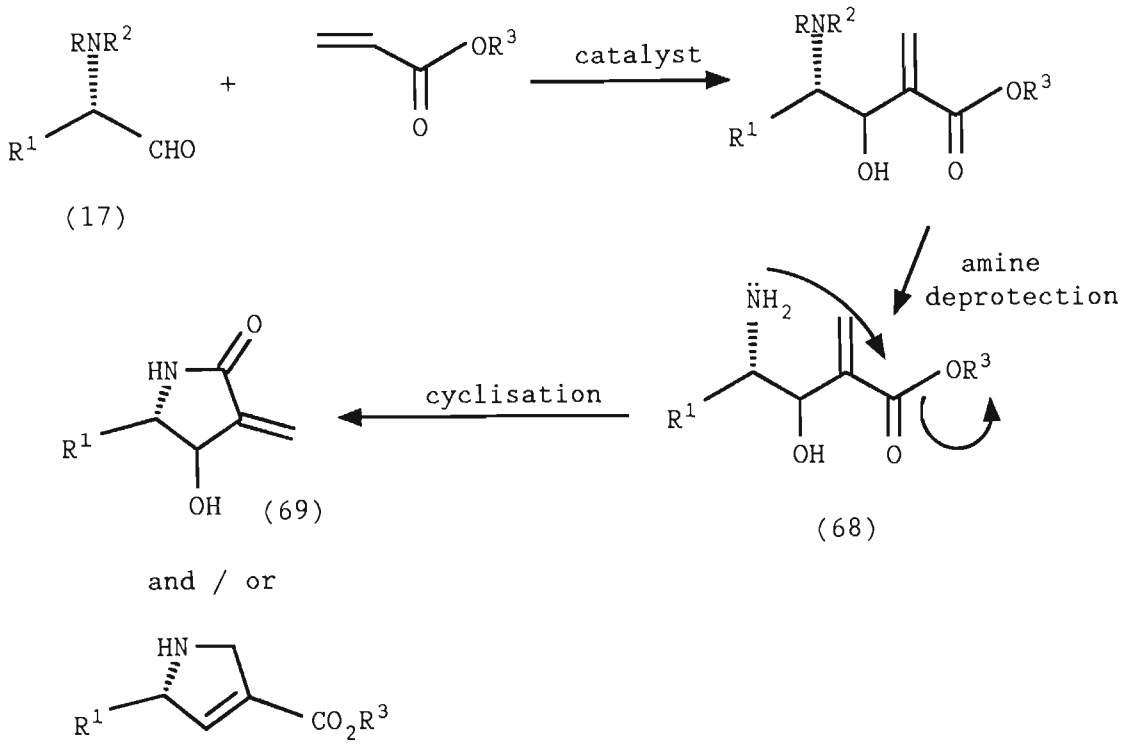
α-Methylene-β-hydroxy-γ-butyrolactones[81] are very interesting compounds for their cytotoxic and anti-tumour activities and for their skin-sensitizing properties. With resident chirality in the aldehyde, (R^1), the potential for suitable precursors (54), with asymmetric induction at C-3, to the α-methylene-β-hydroxy-γ-butyrolactones[81] (65/67), exists if one utilises an α-substituted, α-alkoxy, i.e., O-protected, aldehyde (16) (SCHEME 12).



SCHEME 12.

1.4.2.1.2 THE α-METHYLENE-γ-LACTAMS

The analogous *N*-protected α-amino aldehydes (17) are viewed as potential precursors to the corresponding α-methylene-γ-lactams[72] (69), *via* cyclization of the intermediate γ-amino esters (68) (SCHEME 13).

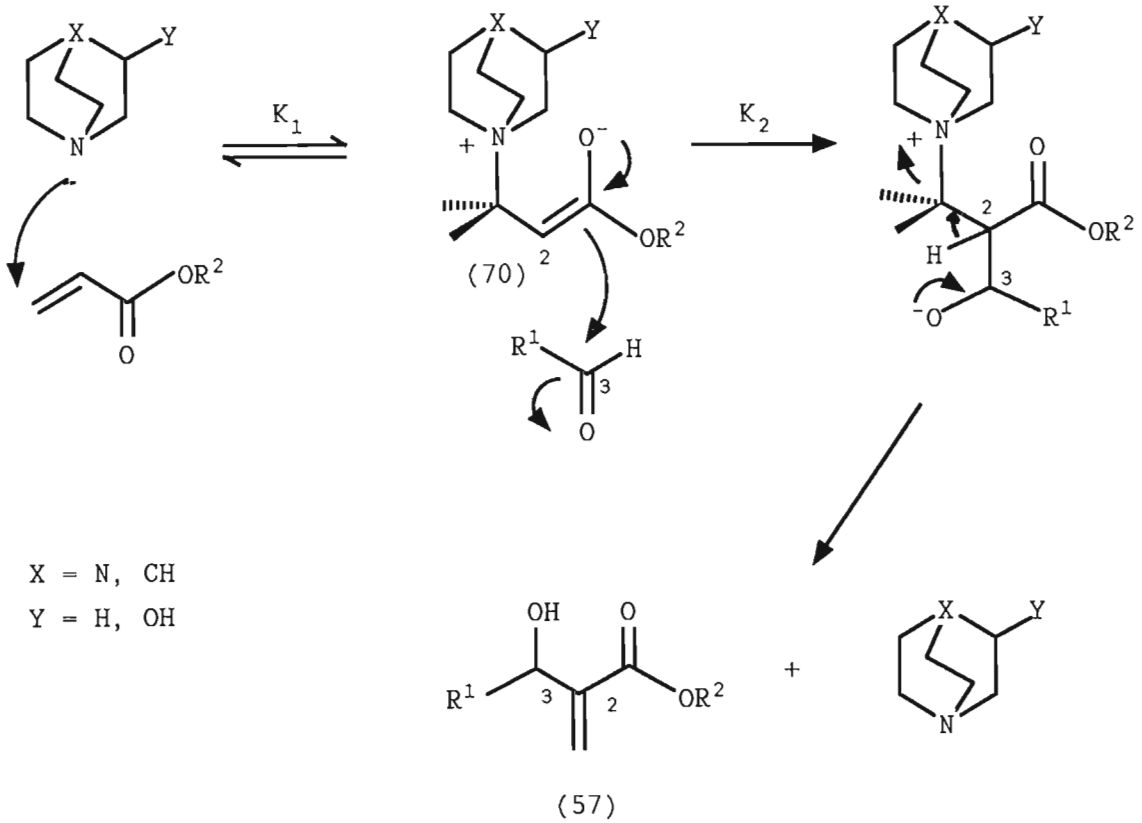


SCHEME 13.

1.4.2.2. ASYMMETRIC ADAPTIONS.

Consideration of the general Baylis-Hillman reaction (EQUATION 10) indicates that the product (57) contains a new chiral centre (racemic) at C-3.

The proposed mechanism[82] involves an addition-elimination sequence. This is initiated by nucleophilic attack of the tertiary amine on the acrylic ester substrate to form a transient dipolar enolate species (70) which subsequently attacks the electrophilic aldehyde at the sp^2 prochiral centre (C-3), i.e., C-2 → C-3 bond formation (SCHEME 14).



SCHEME 14.

Besides the use of DABCO (56), other tertiary cyclic amines such as quinuclidine (71) and (±)-3-quinuclidinol[83] (72) (FIGURE 12), as well as other non-cyclic tertiary amines, such as triethylamine,[84] have been employed by other researchers.

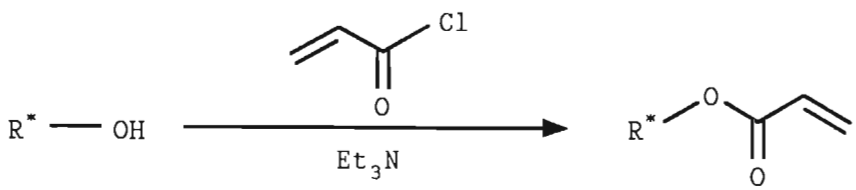
(71) (72)

FIGURE 12.

Thus,:

(1) In view of the abundance of naturally occurring optically active basic compounds (alkaloids, amino acids),

(2) The availability of α-hydroxy acids and alcohols, (from natural sources) which can be converted to the corresponding acrylates (EQUATION 12),
various researchers have attempted to induce chirality in the Baylis-Hillman reaction product (57) by use of the following:
(a) chiral catalysts
(b) chiral α,β-unsaturated (β-unsubstituted) systems.



EQUATION 12.

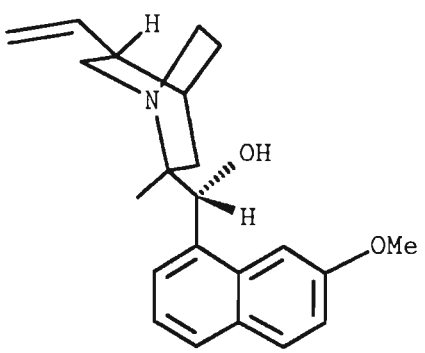
Since the present investigation is based directly on stereo-selective studies in the Baylis-Hillman reaction, it is relevant at this stage to put a perspective on previous attempts toward the achievement of this goal.

1.4.2.2.1 THE USE OF CHIRAL CATALYSTS.

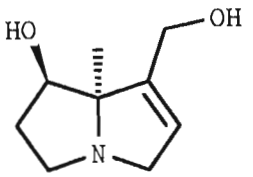
Preliminary studies on the use of chiral catalysts in the Baylis-Hillman reaction by Drewes *et al.*[70] were disappointing in that low e.e's were obtained (TABLE 1).

TABLE 1: Use of chiral catalysts for chiral induction.

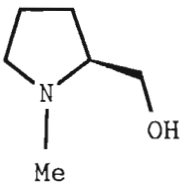
CATALYST	ALDEHYDE	SUBSTRATE	TIME (days)	% e.e.
i) Brucine	CH_3CHO	$CH_2=CHCOCH_3$	4.75	8
ii) Cinchonidine	CH_3CHO	$CH_2=CHCOCH_3$	4.50	10
iii) Quinidine	CH_3CHO	$CH_2=CHCOCH_3$	7.0	12
iv) Quinine (73) (FIGURE 13)	CH_3CHO	$CH_2=CHCOCH_3$	4.5	8
v) Retronecine (74) (FIGURE 13)	$4\text{-}NO_2\text{-}C_6H_4CHO$	$CH_2=CHCOCH_3$	30	0
vi) Retronecine (74) (FIGURE 13)	$4\text{-}NO_2\text{-}C_6H_4CHO$	$CH_2=CHCO_2CH_3$	30	11
ii) (S)-(-)-N-methyl prolinol (75) (FIGURE 13)	CH_3CHO	$CH_2=CHCOCH_3$	4	0



(73)



(74)



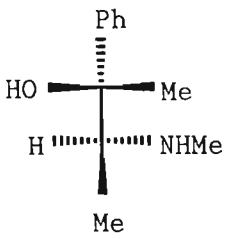
(75)

FIGURE 13.

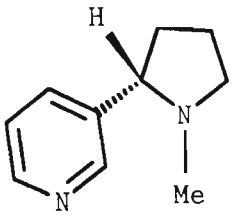
Further studies by Isaacs and co-workers[85] led to similar results, that is, low e.e's, even in the presence of a chiral solvent. Under conditions of high pressure, they[85] obtained the following results (TABLE 2) in reactions between acrylonitrile and acetaldehyde.

TABLE 2: Enantiomeric excess in reactions between acrylonitrile and acetaldehyde in the presence of chiral bases or solvent.

BASE/SOLVENT	p/kbar	T/°C	TIME (h)	YIELD (%)	% e.e.
(-) Quinine (73) (FIGURE 13)	9	60	48	0	-
1R-2S-N-methylephedrine (76) (FIGURE 14)	9	36	100	18	10
S(-)-nicotine (77) (FIGURE 14)	9	35	45	15	11
S(-)-1-methylpyrrolidenyl-methanol	9	40	74	28	17
(±) 3-hydroxyquinuclidine (72) in ethyl-L-(+)-lactate (FIGURE 12)	5	25	24	81	3



(76)



(77)

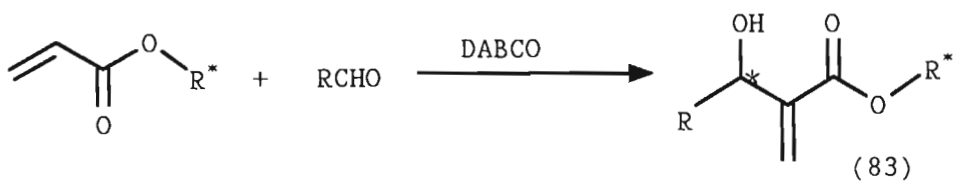
FIGURE 14.

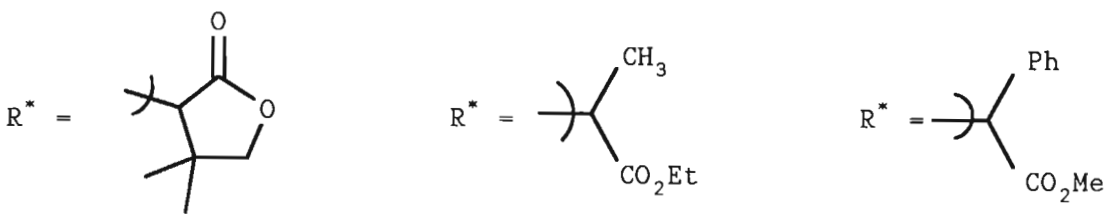
Considering the proposed mechanism[82] of the Baylis-Hillman reaction (SCHEME 14), the low enantiomeric excesses obtained were attributed to the fact that the base attached to the β-carbon is too remote from the reaction centre to exert significant influence on the stereochemical outcome of the reaction. The added disadvantage noted was that, in these reactions (TABLE 2), the chiral bases were all poor catalysts for the reaction and thus yields were low, tending even to zero (TABLE 2).

1.4.2.2 THE USE OF CHIRAL ACRYLIC ESTERS.

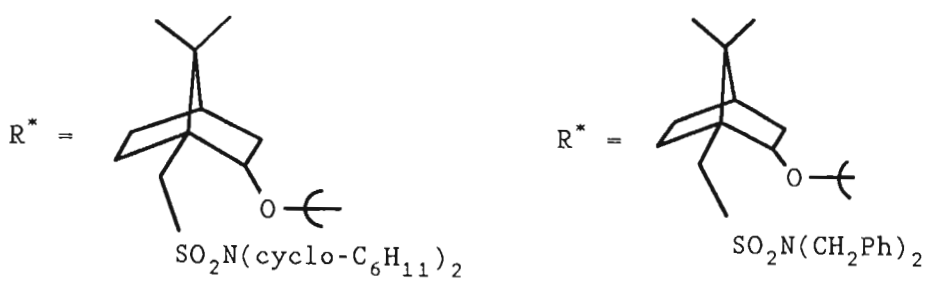
Utilisation of a chiral acrylic ester could result in preferential enantiofacial attack at the aldehyde, that is, an enantioface-differentiating reaction, after removal of the chiral auxiliary.

The optically active acrylic esters of (R)-(-)-pantolactone, (S)-(-)-ethyl lactate and (R)-(-)-methyl mandelate (78)-(80) have been utilised in recent investigations[86] (SCHEME 15).





(78) (79) (80)



(+) - ISOMER (81a)

(-) - ISOMER (81b)

(82)

SCHEME 15.

However, as in the case with the use of chiral catalysts, very low e.e.'s were obtained (TABLE 3).

TABLE 3: Reaction of chiral acrylates (78)-(82) with achiral aldehydes RCHO.

ENTRY	ACRYLATE	ALDEHYDE RCHO	PRODUCT (%YIELD)	TIME (days)	%d.e.	% e.e.[b]
1	78	CH_3CHO	83	-	-	10
2	79	CH_3CHO	83	-	-	6
3	80	CH_3CHO	83	-	-	7.5
4	81b	Cl_3CCHO	83(68)	2	25	-
5	81a	CH_3CH_2CHO	83(60)	21	7(70)[a]	-
6	81b	CH_3CH_2CHO	83(54)	24	9	-
7	81a	$cycloC_6H_{11}CHO$	83(56)	24	26	-
8	81a	$(CH_3)_2CHCHO$	83(63)	15	20	-
9	81a	$p\text{-}NO_2\text{-}PhCHO$	83(61)	30	9	-
10	81a	PhCHO	83(58)	28	10	-
11	82	CH_3CH_2CHO	83(74)	7	6	-
12	82	PhCHO	83(71)	5	8	-

[a]After crystallisation from hexane.

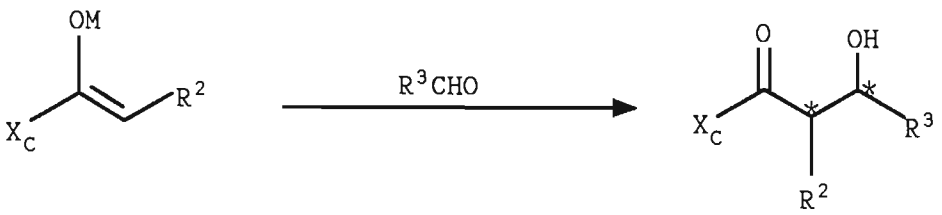
[b]Obtained from the benzyl esters (84) after trans-esterification of the initial coupling products.

More recently, Jensen and Roos[87] assessed the efficiency of a selection of camphor-derived acrylates[88] (81/82) which possess the favourable features for discriminatory ability (SCHEME 15).

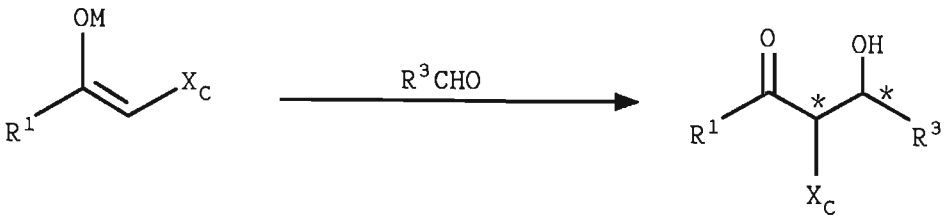
Their results, listed in TABLE 3 above, whilst overall somewhat disappointing, represent the best induction reported at the time.[89]

1.5 AIMS OF THE PRESENT INVESTIGATION.

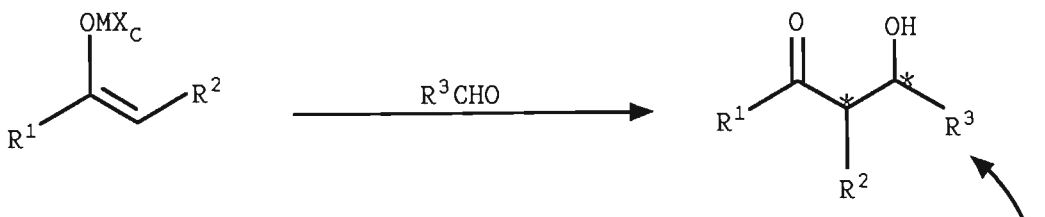
The application of asymmetric synthesis through nucleophilic reaction of chiral enolates commands a great deal of current interest. For the chiral moiety X_c, a number of positional permutations exist for substitution of this ligand on the enolate system (EQUATIONS 13-16).



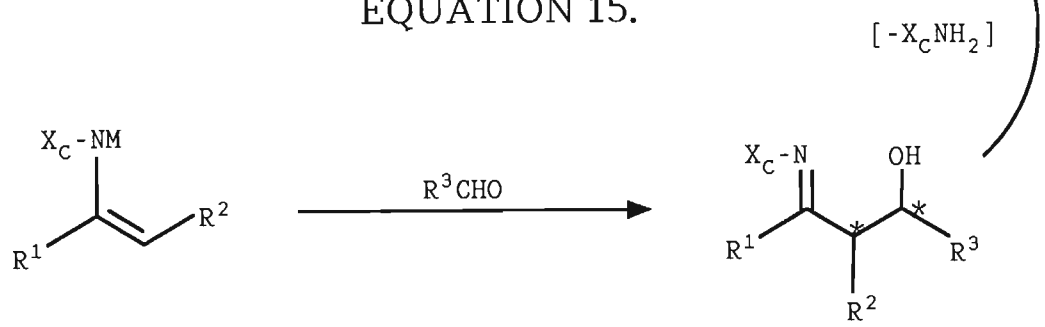
EQUATION 13.



EQUATION 14.



EQUATION 15.

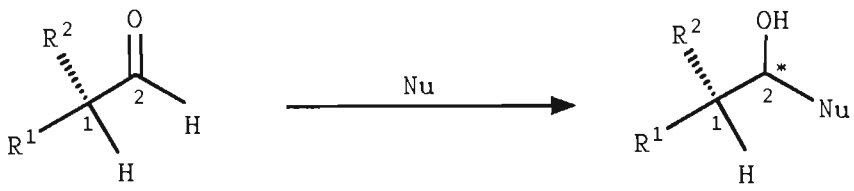


EQUATION 16.

When Xc is attached to the carbon framework (EQUATIONS 13 and 14), the chiral moiety (auxiliary) is either an integral part of the molecule (e.g., chiral ketones), or the chiral ligand can be removed after the desired chirality transfer has been achieved.

Two additional options for emplacement of chirality in the enolate moiety are the design of chiral metal centres (EQUATION 15) and the utility of chiral metalated enamines as enolate synthons (EQUATION 16).

Addition of an achiral carbon nucleophile to an α-substituted α-chiral (or racemic) aldehyde (or ketone), results in the creation of a new chiral centre, that is, 1,2 (relative) asymmetric induction (EQUATION 17).



EQUATION 17.

In this case, the diastereoselectivity depends on the chiral substituted aldehyde (or ketone) which gets incorporated in the product.

In its simplest form, the Baylis-Hillman reaction involves the tertiary amine-catalysed reaction of an activated vinyl carbanion (achiral enolate) with an aldehyde (EQUATION 10).

As stated earlier, protected α-hydroxy and α-amino aldehydes, readily available in optically active form from natural sources, are versatile intermediates in organic synthesis.

In their attempts to establish a viable route to the stereoselective synthesis of α-methylene-β-hydroxy-γ-alkoxy esters, Scolastico and co-workers[68] adopted the approach of an aldol-type condensation between an α-alkoxy aldehyde and a synthetic equivalent of a vinyl carbonyl α-anion (SCHEME 10).

We reasoned that an alternative and obviously simpler approach to the latter multifunctional compounds would be to utilize the Baylis-Hillman reaction to generate the appropriate vinyl anion. Furthermore, application of this reaction to the present synthesis was particularly appealing because, *inter alia*:

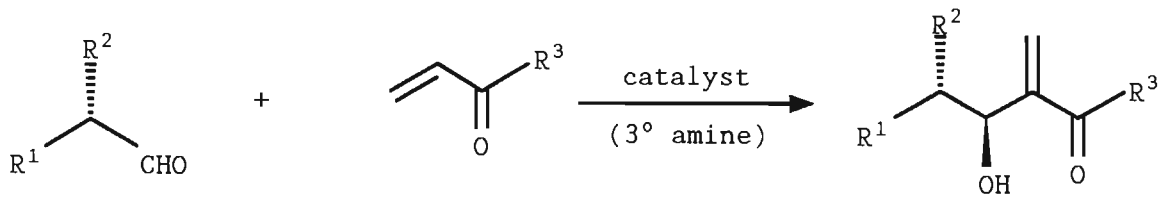
(1) of its relative ease of implementation, which avoids the vaguaries of low temperature metal-enolate (carbanion)

reactions,

(2) it obviates the need for masking and subsequent release of the acrylic portion.

Consequently, the AIMS of this investigation were thus the following:

(1) Reactions of α-substituted α-CHIRAL (homochiral or racemic) aldehydes (85), (i.e. α-alkoxy and α-amino), with ACHIRAL α,β-unsaturated (β-unsubstituted) activated vinyl systems (86), in the Baylis-Hillman reaction, i.e., under *metal-coordination free* reaction conditions (EQUATION 18).



(85) (86) *ANTI*

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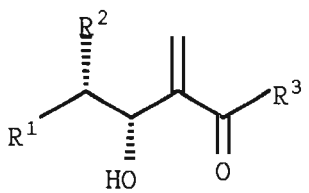


SYN

"ALKOXY" $\begin{cases} R^1 = \text{alkyl, aryl} \\ R^2 = \text{alkyl, } O\text{-alkyl, } O\text{-alkoxyalkyl} \end{cases}$

"AMINO" $\begin{cases} R^1 = \text{alkyl} \\ R^2 = N\text{H(alkyl), } N\text{(alkyl)}_2 \end{cases}$

$R^3 = OCH_3$ (86 A)

$R^3 = CH_3$ (86 B)

$R^3 = O^tBu$ (86 C)

$R^3 = {}^tBu$ (86 D)

EQUATION 18.

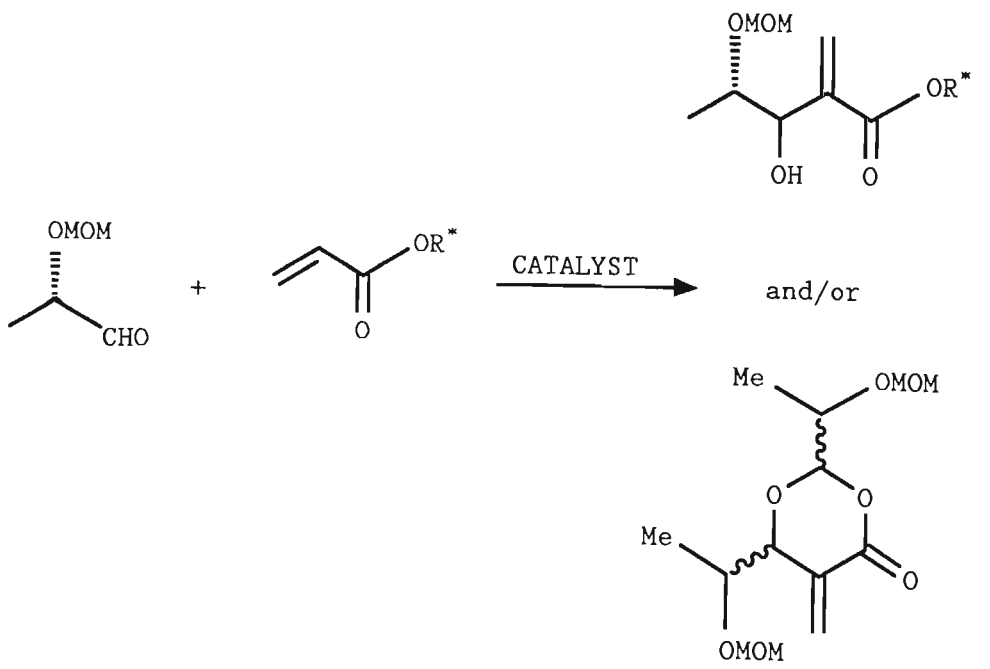
(2) Establishment of the viability of the reaction and its intrinsic diastereoselectivity. This would obviously necessitate establishment of a method for the determination of diastereomeric ratios.

(3) Effects of variation of the parameters R^1, R^2 and R^3 on the stereochemical course (diastereoselectivity) of the coupling reaction. Consequently, this would entail preparation of a variety of selected starting materials.

(4) Assignment of the stereosubstructure (*anti*, *syn*) (relative configuration) of the diastereomeric products.

(5) Possible applications of selected adducts (diastereomer/s) in further elaboration, e.g., the α-methylene-β-hydroxy-γ-butyrolactones (65/67), (and/or γ-lactams 69).

(6) Attempts to optimise (enhance) the diastereoselectivity by the use of CHIRAL acrylic esters, i.e., double asymmetric induction (double diastereoselection) (EQUATION 19).



(244)

EQUATION 19.

CHAPTER 2

2. REACTIONS OF THE α-ALKOXY/ALKYL ALDEHYDES.

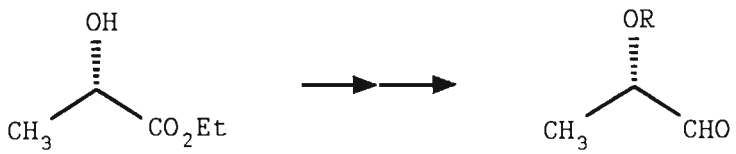
2.1 PREPARATION OF THE STARTING MATERIALS.

It was proposed that maximisation of the diasteroeomeric transition state energy difference, for example, by steric effects, would result in high stereoselectivity.

Thus, the most direct way to achieve this goal on the system studied is by introduction of bulk effects *via* R^1, R^2 and R^3 variations. However, such choices were limited by the relative adaptability to practical situations. This area of study therefore necessitated the preparation of a few starting materials of defined steric demand. Some practical drawbacks were experienced and these will be discussed in the relevant sections.

2.1.1 THE α-ALKOXY ALDEHYDES.

It has been shown by several workers that O-protected α-hydroxy lactaldehydes (16) are accessible in optically active form from the readily available optically pure (S)-(-)-ethyl lactate (87a) (EQUATION 20).



(87a) (16)

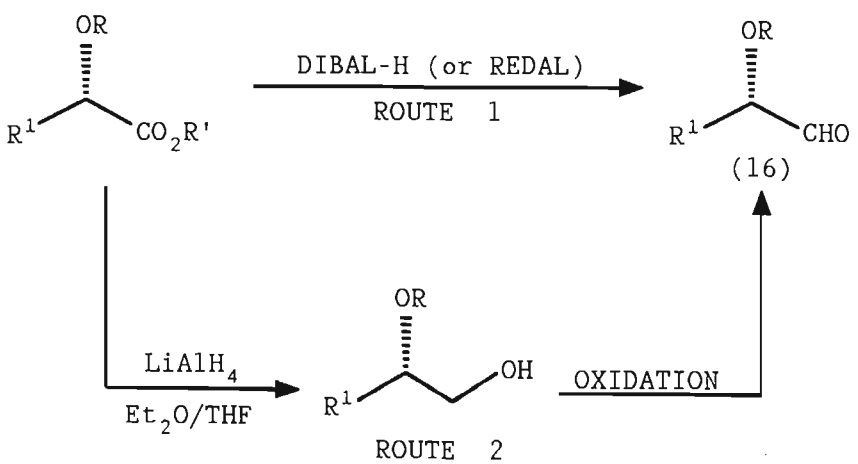
EQUATION 20.

2.1.1.1. HYDROXYL PROTECTING GROUPS.

A suitable protecting group should satisfy the following requirements:[90]

(1) Incorporation under mild conditions, especially conditions that do not affect the optical purity of the substrate.
(2) Stability under the reaction conditions.
(3) Deprotection under mild conditions, with no effect on the substrate.

α-Hydroxy and α-amino acids (or esters), that is, nature's chiral "pool"[4], are common starting materials to produce O-protected α-hydroxy aldehydes. Having protected the hydroxyl group, two possible routes to obtain the aldehydes can, in general, be considered (SCHEME 16).



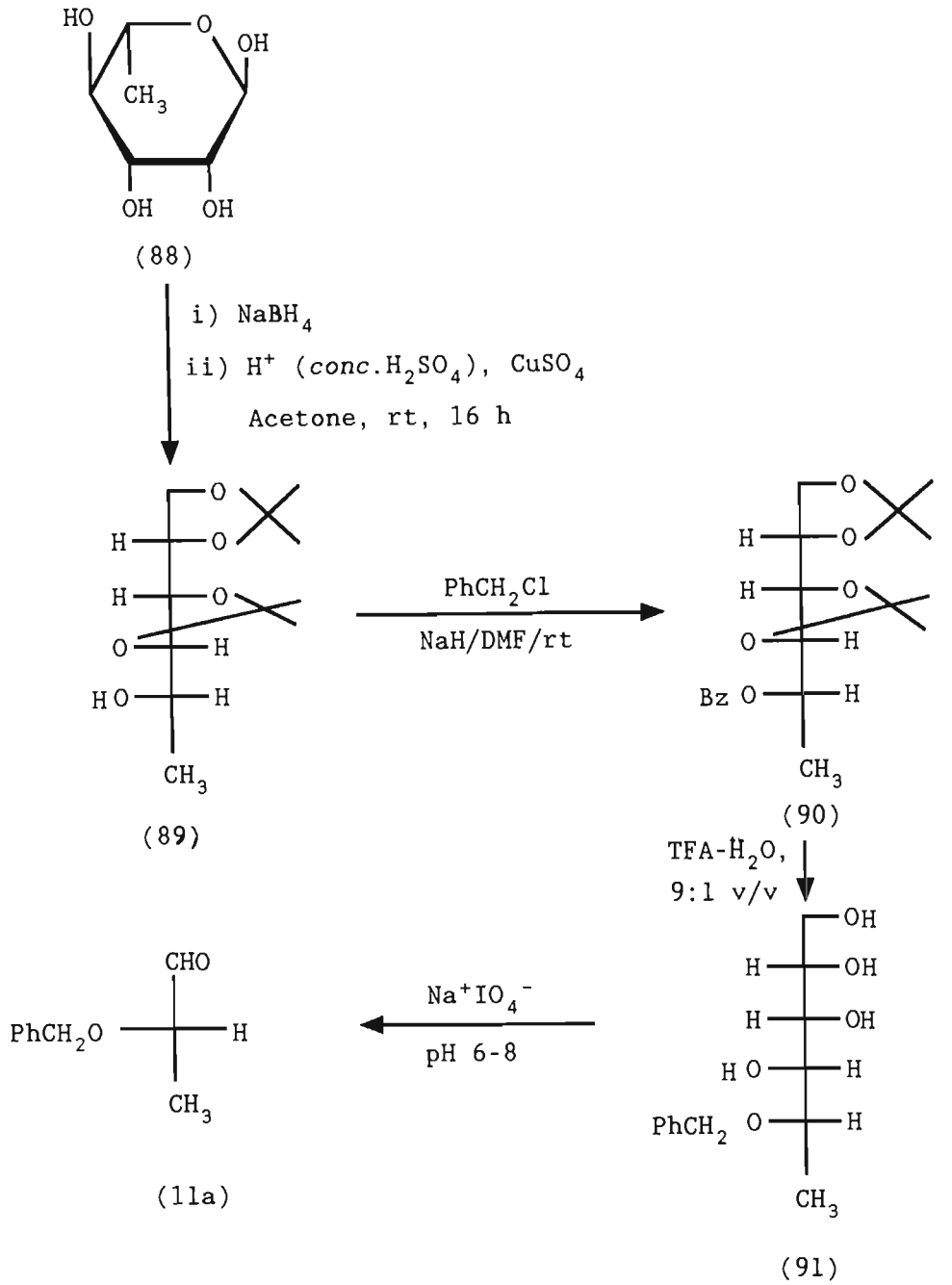
SCHEME 16.

ROUTE (1) is more attractive because it involves a single step, viz., diisobutylaluminium hydride[91] (DIBAL-H) reduction of the ester directly to the aldehyde, which can be achieved at low temperatures. However, a mixture of the desired aldehyde, alcohol and starting ester is often obtained.

ROUTE (2) first involves reduction of the ester with lithium aluminium hydride[92] ($LiAlH_4$) to the alcohol, followed by an oxidation to the aldehyde. Various oxidising reagents, for example, PDC,[93] PCC,[94] Jones',[95] Collins',[96] oxalyl chloride-DMSO (Swern oxidation[97]) and periodinane (Dess-Martin[98] oxidation), have been reported in the literature to effect the latter transformation with varying degrees of success.

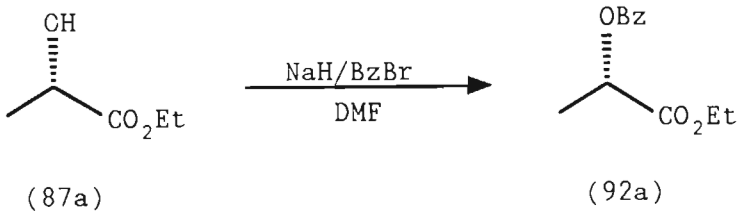
The benzyl protecting group was chosen as the first possibility.

Various researchers[99] have utilised optically pure (S)-(-)-2-(benzyloxy)propanal (11a) as a synthetic intermediate for further elaboration in natural product synthesis and thus various routes to the desired aldehyde have been reported.[99] Baker and Hawkins[100] obtained compound (11a) in 84% yield starting from commercially available (L)-rhamnose (88) (SCHEME 17).



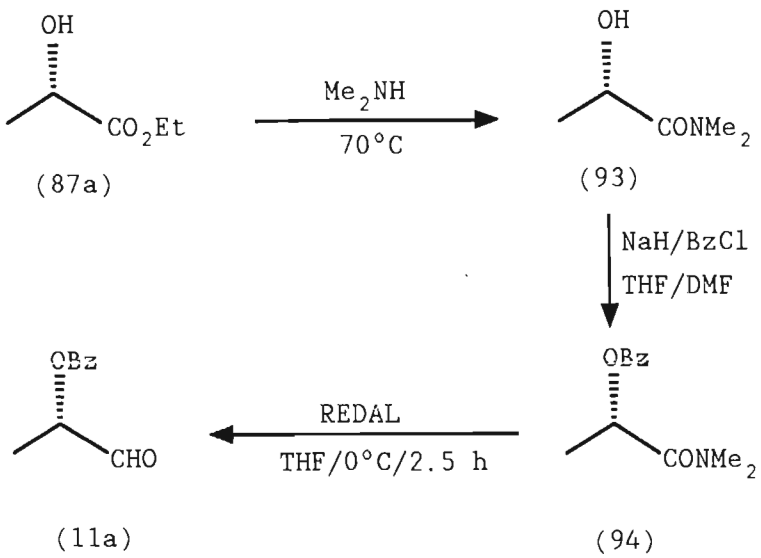
SCHEME 17.

Direct benzylation of optically active ethyl lactate (87a) under basic conditions affords the desired α-alkoxy ester (92a) only in low yield[101] and is accompanied by considerable racemization[102] (EQUATION 21). However, Terashima and co-workers[103] were able to produce the target molecule (11a) without racemization, in 90% yield (SCHEME 18).



(87a) (92a)

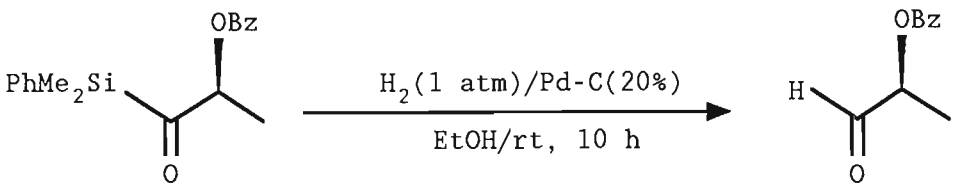
EQUATION 21.



(87a) (93) (11a) (94)

SCHEME 18.

More recently, Cirillo and Panek[104] reported an efficient and selective desilylation of racemic *syn*-α,β-dialkoxy-acyl-dimethylphenylsilanes, e.g. (95) bearing benzyl or BOM protecting groups, to produce the corresponding aldehydes, for example (11), (in racemic form), by catalytic hydrogenolysis (EQUATION 22).



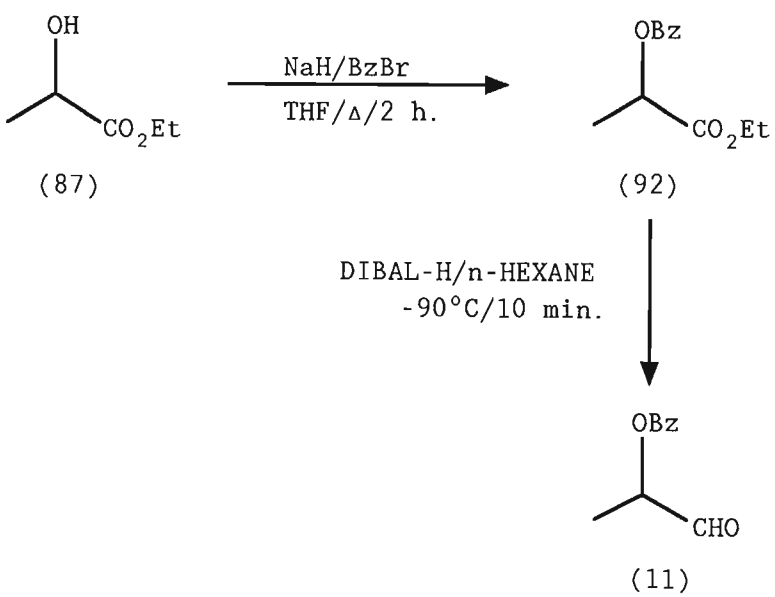
(95) (11)

80% YIELD

EQUATION 22.

The selective silicon-carbonyl bond cleavage can be carried out in the presence of protecting groups known to be labile to catalytic hydrogenolysis, such as the benzyl and BOM protecting groups. Acid-sensitive protecting groups, such as acetonides and MOM ethers are also left unaffected.

In this study, 2-(benzyloxy)propanal (11) was prepared in racemic form from (±)-ethyl lactate (87) *via* benzylation with sodium hydride/benzyl bromide, followed by reduction of the ester (92) with diisobutylaluminium hydride[91] (SCHEME 19).

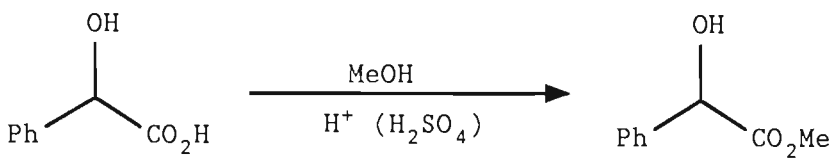


(87) (92) (11)

SCHEME 19.

Purification of the crude aldehyde (11), either by distillation or flash column chromatography,[105] led to an overall yield of 35%.

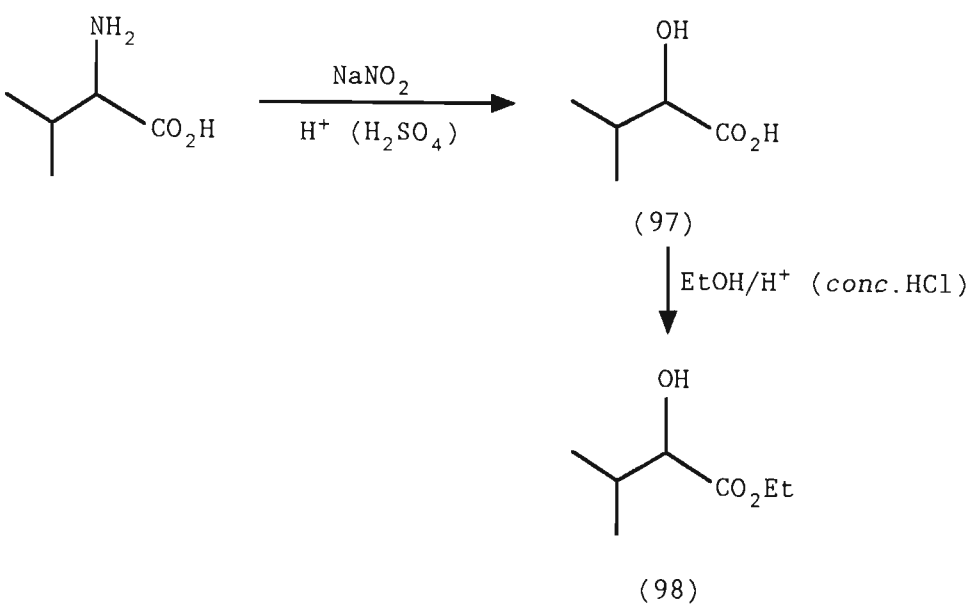
Similarly, (±)-methyl mandelate (96) was obtained from racemic mandelic acid, by esterification (EQUATION 23). The crude ester (96), was subsequently used without further purification.



(96)

EQUATION 23.

(±)-2-Hydroxy-3-methylbutyric acid (97a) was obtained in 63% yield by a literature procedure[106a] starting from (DL)-valine. The crude acid (97) was subsequently esterified[106b] to the corresponding ethyl ester (98) (SCHEME 20).



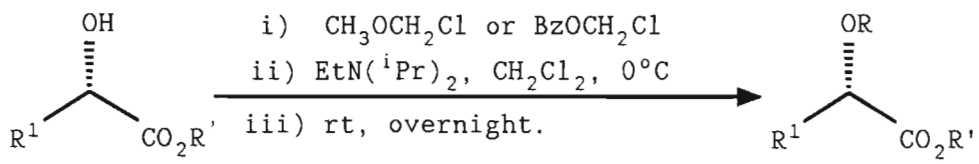
(97)

(98)

SCHEME 20.

The ester (98) was obtained in 59% yield after fractional distillation.

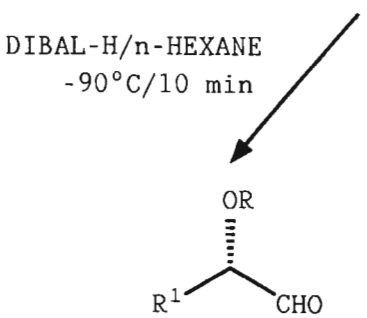
Protection of the resulting α-hydroxy esters was then carried out using the method of Banfi *et al.*[68] for introduction of the MOM and BOM protecting groups, respectively (SCHEME 21).



(87), (96) and (98) (99) - (103)

(87) R^1 = Me, R' = Et
(96) R^1 = Ph, R' = Me
(98) R^1 = ^{i}Pr, R' = Et

(99) R^1 = Me, R = MOM, R' = Et
(100) R^1 = Me, R = BOM, R' = Et
(101) R^1 = Ph, R = MOM, R' = Me
(102) R^1 = ^{i}Pr, R = MOM, R' = Et
(103) R^1 = ^{i}Pr, R = BOM, R' = Et



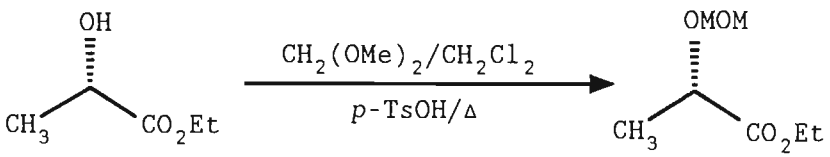
(104) - (108)

(104) R^1 = Me, R = MOM
(105) R^1 = Me, R = BOM
(106) R^1 = Ph, R = MOM
(107) R^1 = ^{i}Pr, R = MOM
(108) R^1 = ^{i}Pr, R = BOM

SCHEME 21.

The resulting O-protected esters [(99)-(103)] were then directly transformed into the corresponding aldehydes using diisobutylaluminium hydride[68] (SCHEME 21). Purification of the crude aldehydes was effected by distillation and/or flash chromatography.[105]

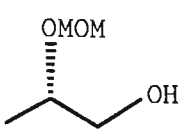
It should be noted that an alternative route to hydroxyl protection with the MOM group involving the use of dimethoxymethane[107] in the presence of a catalytic amount of *p*-toluenesulfonic acid, was also used (EQUATION 24). However, yields made this alternative less viable.



(87a) (99)

EQUATION 24.

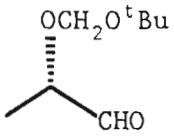
The alternative route to the aldehyde (104), ROUTE 2 (SCHEME 16), by Swern oxidation[97] of the alcohol[68] (109), was also carried out. However, this only afforded the desired aldehyde in 26% yield.



(109)

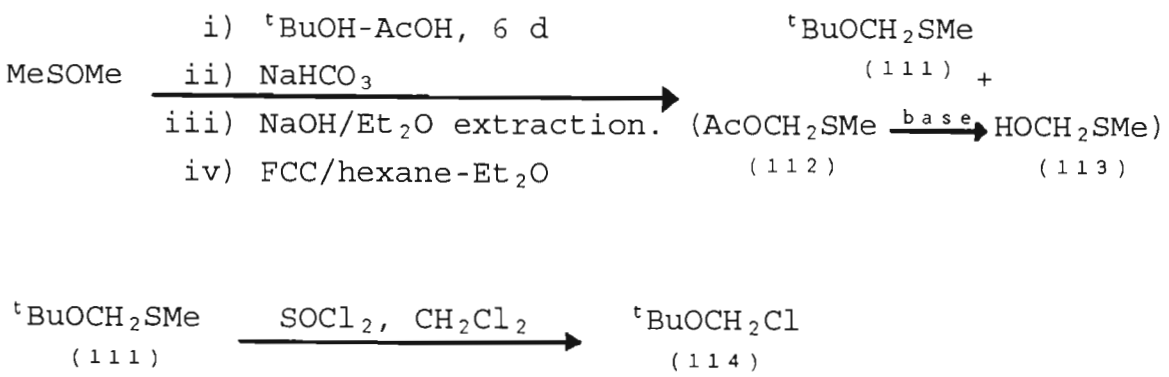
2.1.1.1.1 ATTEMPTED SYNTHESIS OF 2-*tert*-(BUTYLOXYMETHOXY)-PROPANAL.

For introduction of bulk effects *via* R^2 variations, an attractive possibility was the synthesis of the aldehyde (110), containing the fairly bulky *tert*-butyloxymethoxy protecting group, which should be available from the readily available (S)-(-)-ethyl lactate (87a).



(110)

However, preparation of the above unknown compound (110), (or even the ester precursor), was not a trivial matter due to difficulties experienced with the synthesis of the "protecting group" reagent, viz., *tert*-butyl chloromethyl ether (114). Of the routes available, the most direct route, that of Jones *et al.*[108] was initially attempted (SCHEME 22).



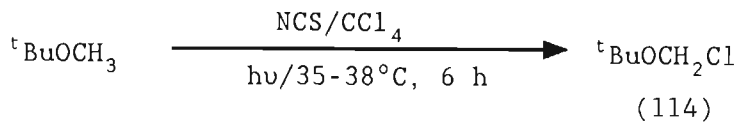
SCHEME 22.

Jones *et al.*[108] have noted that the desired product (111) was invariably acompanied by substantial amounts of (112), from which it could not be separated easily. However, subsequent conversion to methylthiomethanol (113) by addition of base, allowed the separation of mixtures of (111) and (113) during the purification step.

However, flash chromatography[105] *surprisingly* failed to yield any of the desired intermediate product (111) despite numerous repeat attempts.

Although correspondence with Jones elicited assistance by way of modifications with the workup procedure, and subsequent purification, the desired *tert*-butoxymethyl methyl sulphide (111) was not obtained.

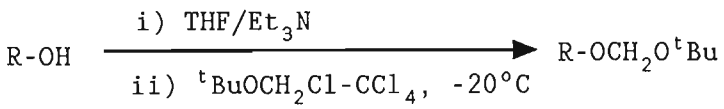
Another reported[109] preparation of (111) involves the photochemical chlorination of *tert*-butyl methyl ether, a satisfactory but somewhat inconvenient method (EQUATION 25).



EQUATION 25.

The above route affords the chloromethyl *tert*-butyl ether (114), directly, as a *solution*, which is claimed[109] to be stable under nitrogen, at room temperature.

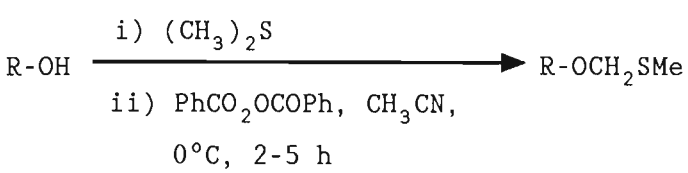
Subsequent treatment of the alcohol substrate with the chloro ether solution (114) affords the protected alcohol (EQUATION 26).[109]



EQUATION 26.

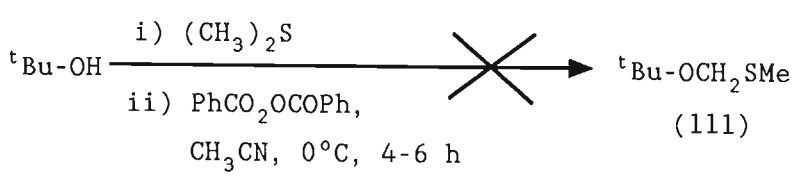
However, the above method[109] when applied to (S)-(-)-ethyl lactate (87a) was also unsuccessful.

A more recent method[110] using mild conditions and which avoids long reaction times and strongly acidic conditions, is shown below (EQUATION 27). Primary, secondary and tertiary alcohols are converted to their corresponding methylthiomethyl ethers under the reaction conditions.[110]



EQUATION 27.

Yet again, application of the above method,[110] after many repetitions, to *tert*-butanol as alcohol substrate, did not afford the target molecule (111) (EQUATION 28).

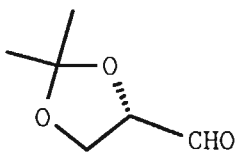


EQUATION 28.

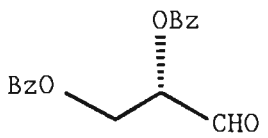
With reference to the literature,[50] an extension to the glyceric aldehyde system (20) and (115) (FIGURE 15) is appealing for two reasons:

(1) The protected forms of optically active glyceraldehyde, that is, both enantiomers, are readily available by simple synthesis from natural sources.

(2) The derived products lend themselves to conversion to a wide variety of useful synthons.



(20)



(115)

FIGURE 15.

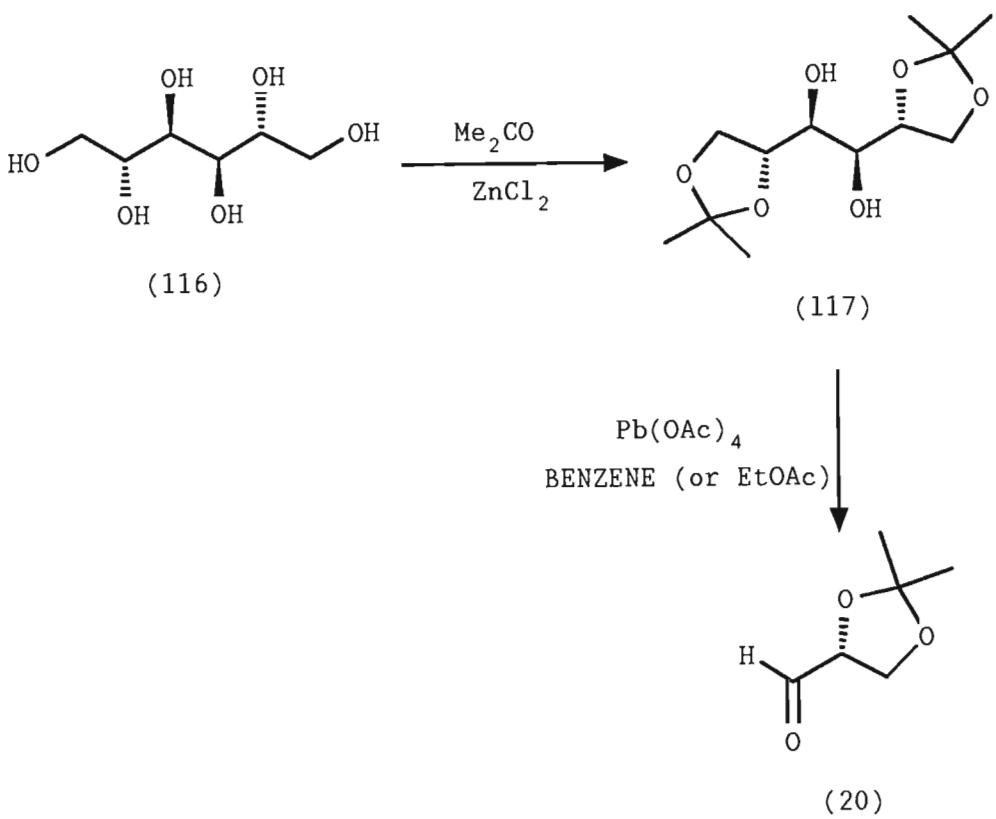
Thus, the synthesis of (R)-2,3-O-isopropylidene glyceraldehyde (20) and the dialkoxy carbonyl system (R)-2,3-O,O-dibenzylglyceraldehyde (115) was undertaken.

The great interest shown by organic chemists in (20) is reflected by the rapidly growing number of relevant publications, including an excellent review,[50] focusing on its preparation and use in stereocontrolled organic synthesis, that have appeared.

The number of reported procedures for obtaining this material (20) bear witness to the generally unsatisfactory nature of existing methods for its synthesis.

The first effective preparation of (20) was reported by Baer and Fischer[111] in 1939. (D)-Mannitol (116), a naturally

occurring and inexpensive polyhydroxylated compound, was used as a starting material. The *bis*-acetonide of (D)-mannitol was prepared. The resulting diol (117) was then cleaved[112] with lead tetraacetate to give (20) (SCHEME 23).

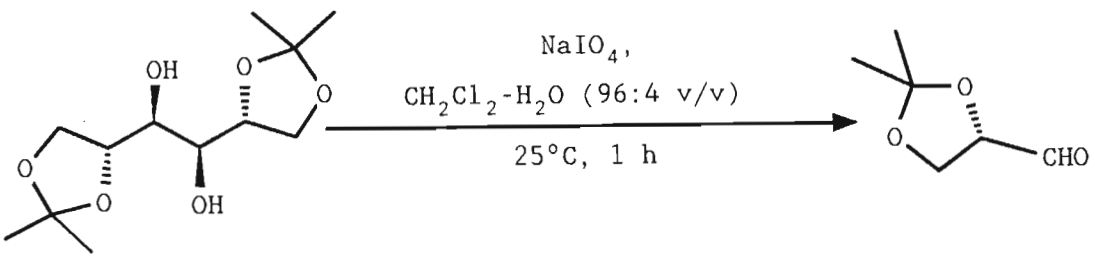


SCHEME 23.

Several modifications of this classical, but still most often applied method have been reported.[113,114]

Modifications of the second stage, dealing with cleavage of the *vic*-diol group in (117), involve replacement of lead tetraacetate by sodium periodate,[114,115] or by catalytic amounts of bismuth derivatives.[50] Jackson[116] reported an improved preparation of the title compound (20), in high optical purity and also in a high chemical yield (91%) by

sodium *meta*-periodate oxidation of the diol (117) in the presence of a small amount of water (4% by volume) (EQUATION 29).



(117) (20)

EQUATION 29.

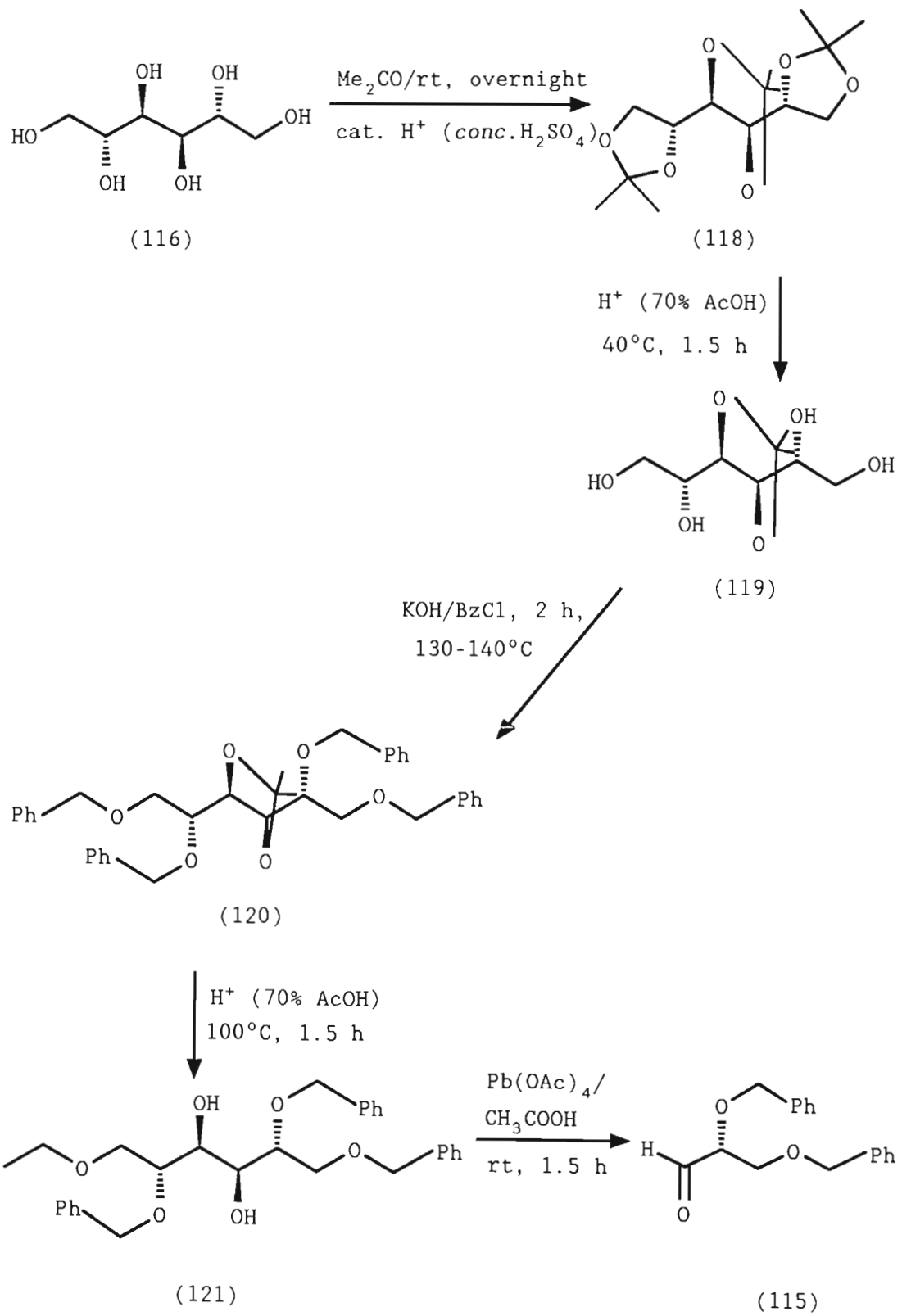
The procedure described by Jackson[116] was employed in our synthesis of (20) (EQUATION 29) and preparation of the diol (117) was carried out as described by Baer,[117] i.e., ketalisation of (D)-mannitol with the acetone/zinc chloride system (SCHEME 23).

However, the desired aldehyde (20) was obtained in only 47% overall yield from (117).

Whereas 2,3-O-isopropylideneglyceraldehyde (20) is most widely used, there are reports[50] of other groups protecting the diol function: O-dibenzyl, O-dimethyl, O-carbonate, O-dibenzoyl and O-cyclohexylidene.

A general approach to the synthesis of O-acylated as well as acetal or O-silylated derivatives of glyceraldehyde was developed.[50]

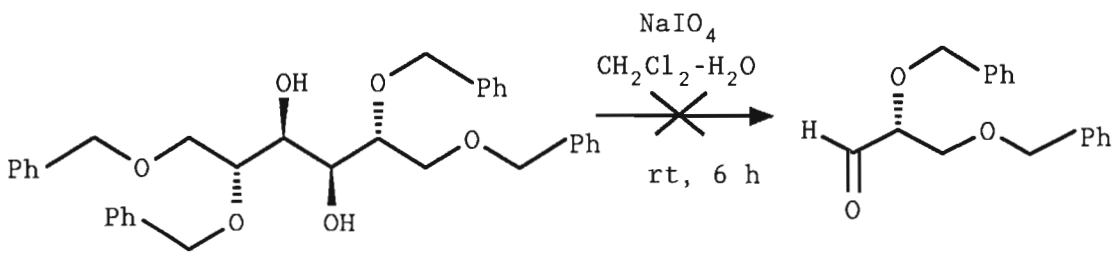
We prepared (R)-2,3-di-O-benzylglyceraldehyde (115) by the literature procedure using (D)-mannitol (116) as starting material (SCHEME 24).


Me2CO/rt, overnight
cat. H+ (conc.H2SO4)
(116)
(118)
H+ (70% AcOH)
40°C, 1.5 h
(119)
KOH/BzCl, 2 h,
130-140°C
(120)
H+ (70% AcOH)
100°C, 1.5 h
Pb(OAc)4/
CH3COOH
rt, 1.5 h
(121)
(115)

SCHEME 24.

Triacetone mannitol (118) was prepared[118] by stirring a mixture of (D)-mannitol (116) in acetone overnight, followed by the usual method of isolation.[119] Subsequent hydrolysis[118] of (118) with acetic acid afforded the 3,4-isopropylidene derivative (119). Benzylation,[120] under standard conditions, afforded the 1,2,5,6-tetra-O-benzyl-3,4-O-isopropylidene-(D)-mannitol (120). Hydrolysis[120] of (120) to the diol (121), followed by oxidative cleavage[120] with lead tetraacetate, afforded the dibenzyl protected aldehyde (115). The crude aldehyde was subsequently purified by chromatography.

It should be noted that an initial attempt to oxidise the diol (121) with sodium *meta*-periodate was unsuccessful, with quantitative isolation of the starting diol, even after prolonged reaction time (6 hours) at room temperature. (EQUATION 30).



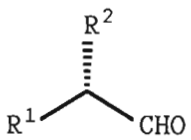
(121) (115)

EQUATION 30.

Ohgo *et al.*[121] also report the preparation of the dialkoxy aldehyde (115) (ENTRY 7) by oxidation of the diol (121) with lead tetraacetate, in benzene as solvent. However, their method of purification involved distillation under very low pressure, (reported boiling point: 143-144/0.003 mm Hg).

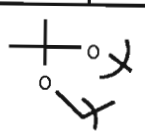
Furthermore, their reported optical rotation on this aldehyde was $[\alpha]_D$= +52°, (*c* 2.0, benzene). Yet again, the lower e.e. obtained by us can be due to racemisation of the aldehyde on exposure to silica gel.

TABLE 4 summarises the various alkoxy aldehydes (85) that were prepared for the present study.



(85)

TABLE 4: Synthesis of the α-alkoxy aldehydes.

ENTRY	ALDEHYDE	R^1	R^2	$[\alpha]_D^{25-28}$	CONFG.	YIELD (%)
1	11	Me	OBz	-	±	35
2	104	Me	OMOM	-12.55°(a)	S	35
3	105	Me	OBOM	-7.35°(a)	S	65
4	106	Ph	OMOM	-	±	57
5	107	^iPr	OMOM	-	±	32
6	108	^iPr	OBOM	-	±	56
7	115	CH_2OBz	OBz	+26.64°(b)	R	61
8	20			+65.53°(b)	R	47

(a) $CHCl_3$

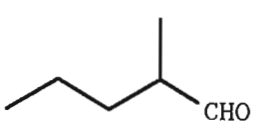
(b) C_6H_6

It is evident that yields of the aldehydes (TABLE 4) were, in general, poor, but no special attempts were, however, made to optimise the yields. The novel aldehyde compounds (106), (107) and (108) (ENTRIES 4, 5 and 6) were characterised by spectroscopy. However, aldehydes (106) and (107) (ENTRIES 4 and 5) were unstable to elemental analysis and/or gave unsatisfactory elemental analyses.

Scolastico and co-workers[68] report an $[\alpha]_D$ value of -13.4° for the optical rotation of the *OBOM*-protected aldehyde (105) (ENTRY 3), which they obtained in pure form after purification by flash chromatography.[105] It can thus be concluded that racemisation must have occurred during its exposure to silica gel during our purification procedure.

2.1.2 THE ALKYL-SUBSTITUTED ALDEHYDE.

In order to determine the effect of a simple, α-alkyl-substituted aldehyde on the diastereoselectivity, the commercially[122] available (±)-2-methyl pentanal (122) was employed.



(122)

2.1.3 ALDEHYDES UTILISED FOR THIS INITIAL STUDY.

FIGURE 16 depicts the various α-alkoxy/methyl-substituted aldehydes that were used in the Baylis-Hillman reaction.

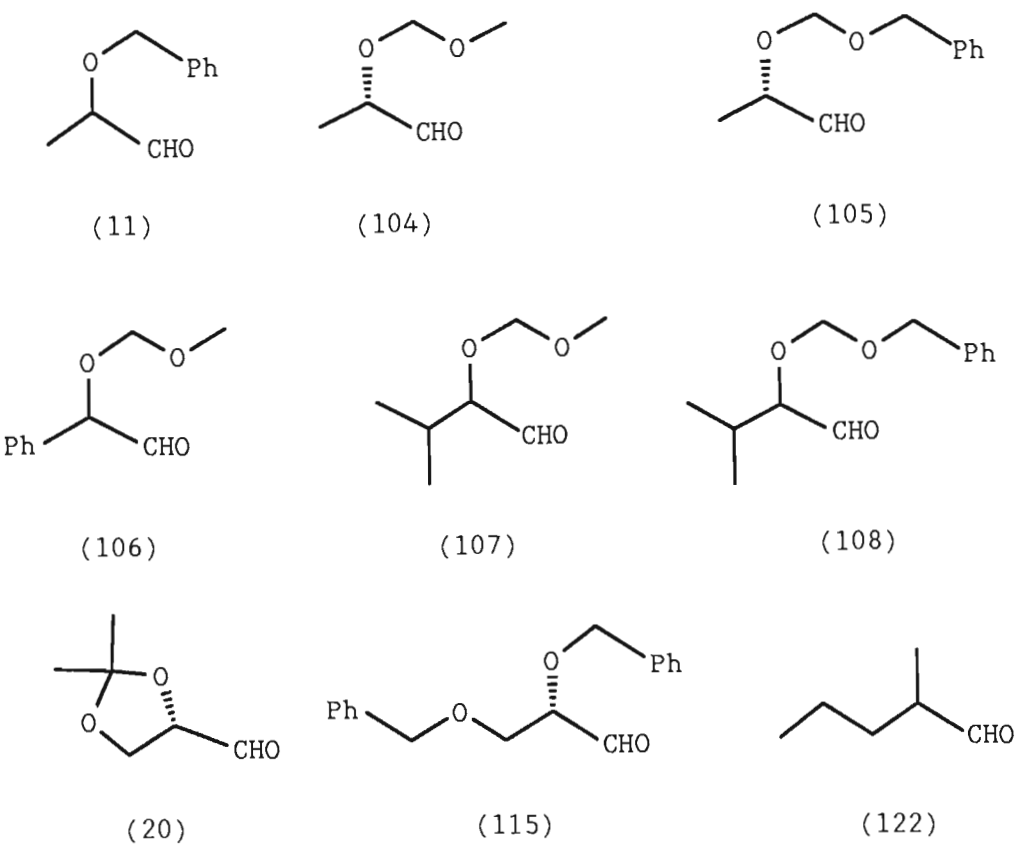


FIGURE 16.

2.1.4 THE ACTIVATED VINYL (α,β-UNSATURATED) SYSTEMS.

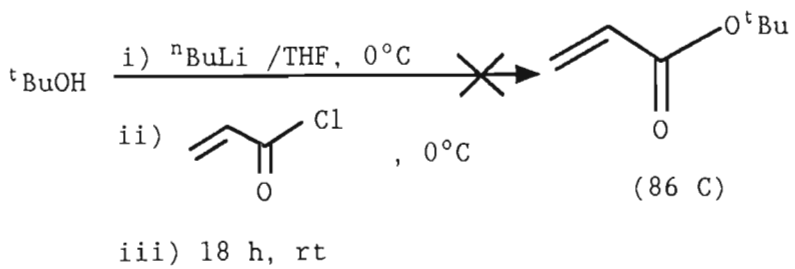
Commercial methyl acrylate (86 A) and methyl vinyl ketone (86 B) (EQUATION 18) (CHAPTER 1) were used.

With respect to the use of bulk effects in the vinyl component, that is, R^3, attention was given to preparation of *tert*-butyl acrylate and the corresponding *tert*-butyl

vinyl ketone.

2.1.4.1 *tert*-BUTYL ACRYLATE.

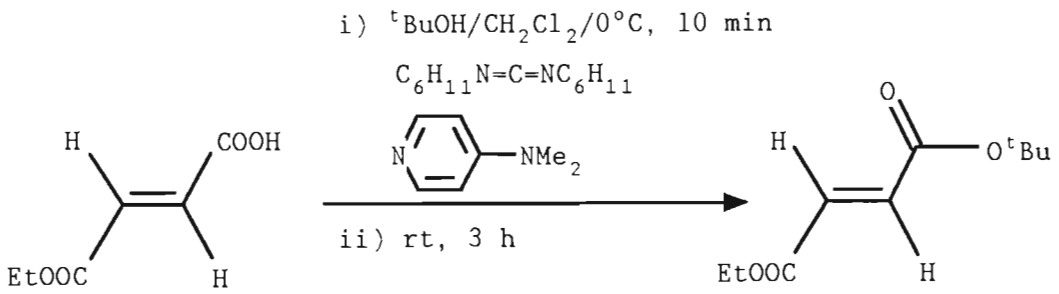
The initial route followed was addition of acryloyl chloride to the lithium salt of *tert*-butanol (EQUATION 31).



EQUATION 31.

However, this procedure failed to yield the desired acrylate. The use of milder bases, for example, triethylamine,[123] remains to be tested.

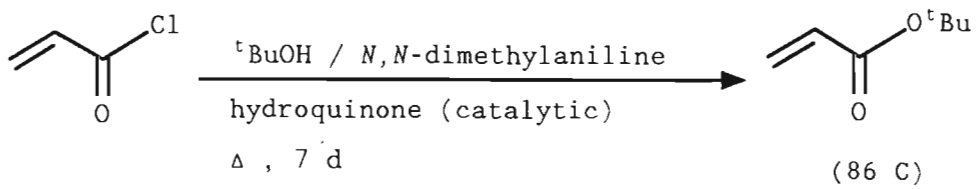
The direct procedure for ester synthesis would, in general, be reaction of the acid with the desired alcohol. In this respect, the procedure[124] for synthesis of *tert*-butyl ethyl fumarate appeared attractive (EQUATION 32).



EQUATION 32.

Application of the above method[124] to acrylic acid was, however, unsuccessful.

tert-Butyl acrylate (86 C) was eventually prepared from acryloyl chloride by an alternative, known procedure[125] (EQUATION 33).

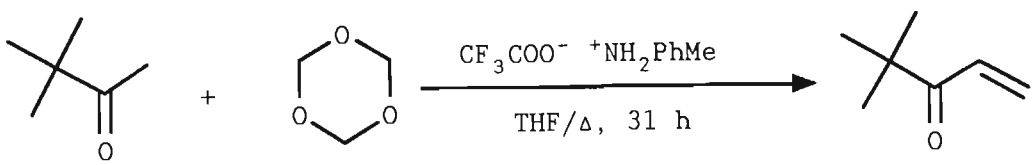


EQUATION 33.

However, other alternative methods[126] are known for its preparation.

2.1.4.2 *tert*-BUTYL VINYL KETONE.

The reported one-step route[127a] to the target molecule, an easy procedure which uses simple reagents, [for example, trioxymethylene (123)], and analogous to the classical Mannich reaction, was carried out (EQUATION 34).



(123) (86 D)

EQUATION 34.

Although the target vinyl ketone was isolated, the yield was too poor for it to be of any practical value in the present investigation.

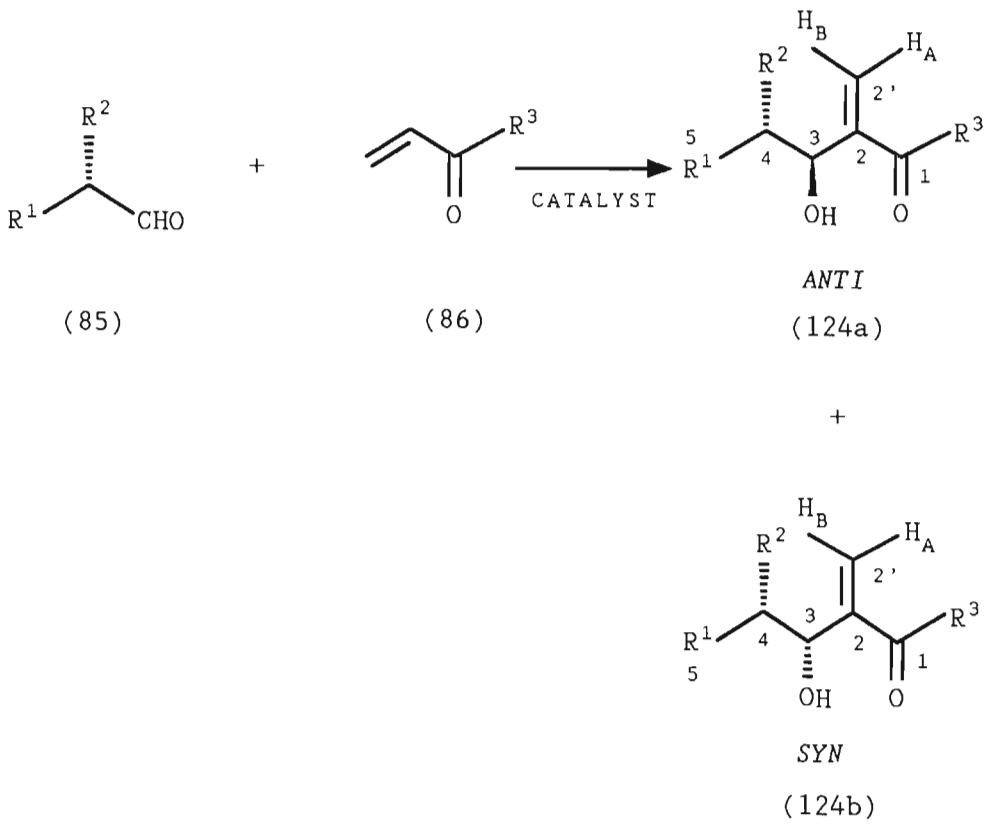
2.2 GENERAL PROCEDURE FOR REACTION OF THE COMPONENTS.

A general procedure involved addition of the aldehyde, neat, to a stirred mixture of the vinyl component, (1.1 equivalents), and catalyst, (0.1-1.0 equivalents), (see TABLE 5), at ambient temperature. In those cases where molar equivalents of catalyst were employed, to obtain synthetically more useful reaction times,[89] a four-fold excess of vinyl component was used. The reactions were stoppered and stirred until ^{1}H n.m.r. indicated consumption of the aldehyde. The mixtures were diluted with dichloromethane, (or chloroform), and washed sequentially with dilute hydrochloric acid and

water. Ratio analysis was then carried out directly on these diastereomeric mixtures before and after isolation by flash chromatography.

2.3 DETERMINATION OF DIASTEREOMERIC RATIOS.

Because these studies involved diastereoselectivity, it was essential to be able to routinely perform the determination of diastereomeric ratios. The ability to achieve this goal with the greatest ease and minimum need for workup, is clearly desirable. Since all of the systems under investigation involved the aldol-related methodology, (i.e., the Baylis-Hillman reaction), a hydroxyl function is always present in the coupled products (124a/b) (EQUATION 18).



(85) (86) (124a)

(124b)

EQUATION 18.

2.3.1 DEVELOPMENT AND USE OF TRICHLOROACETYLISOCYANATE (TAI).

The more established, published methodologies of determining diastereomeric ratios (d.e.'s) include GC/MS analysis of acetates, trifluoroacetates and silyl ethers. These methods generally suffer from the drawback of the need to purify either the isomer mixture or derivatives thereof.

The performance of *in situ* reactions in n.m.r. (sample) tubes represents both optimum utilization of n.m.r. spectroscopy for the study of chemical reactions and for structural assignment of n.m.r. spectra. An exploitation of *in situ* reactions using n.m.r. spectroscopy for structural analytical purposes is less common. In this case, reaction of the investigated substance is carried out with a known reagent. The induced, characteristic changes of the spectrum usually enable structure identification of the reaction centre as well as of its closest proximity. The amount of information on the structure obtained is proportional to the total change of the chemical shifts and coupling constants.

The structure determination of alcohols is a classical structural problem that has strongly stimulated the application of *in situ* reactions in an n.m.r. sample tube. This involves:

(1) determination of the number of OH groups,
(2) classification of the OH groups, (primary, secondary or tertiary, that is, determination of the number of α-CH protons), and
(3) character determination of the α-carbon atom and the relative determination of substituents of the OH group.

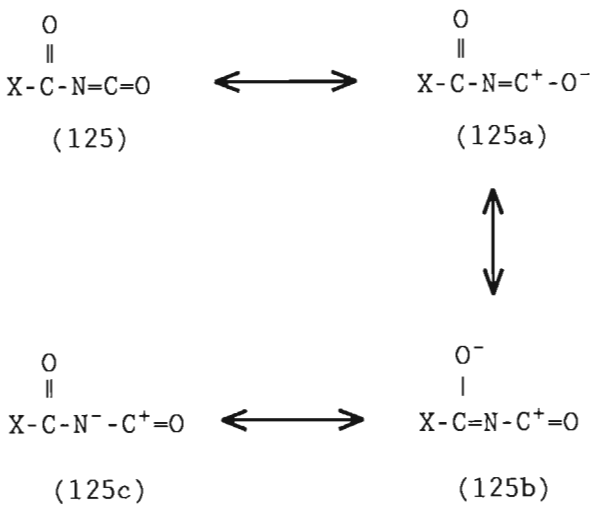
This problem is solvable, in principle, by means of ^{1}H n.m.r. spectroscopy, by direct identification of the corresponding spin systems, with the assignment of the OH signals

by decoupling, exchange experiments, or by variation of concentration, temperature or solvent. However, these procedures are suitable only if it is possible to decrease the mobility of the OH protons so that their long range interactions may be observed. Often these procedures fail, owing to the absence of structurally defined OH signals or to the insufficient selectivity of the α- or β-shifts with respect to the OH, for example, in the application of lanthanide shift reagents. In such instances, ^{1}H n.m.r. spectroscopy makes use of preparative transformations[128] of the O-*H* groups to the more easily defined O-*R* groups (for example, acetylation or benzoylation, dichloroacetylation, formylation or trifluoroacetylation in combination with ^{19}F n.m.r., methylation or trimethylsilylation in combination with ^{29}Si n.m.r., or acylation with optically active acids). Consequently, structurally characteristic acylation or alkylation shifts of the acyl or alkyl groups are usually observed. However, all of these procedures[128] suffer from the following disadvantages:

(1) They require a relatively large amount of substrate.
(2) In a number of polyfunctional cases, they can lead to formation of products which have no evident relationship to the starting material.
(3) They often fail owing to low reactivity of the hydroxy group.
(4) With a very small amount of unknown substrate for derivatization, (less than 10 mg), the preparative methods cannot be applied.

In principle, all these drawbacks are eliminated by *in situ* acylations.

The reactions of acyl isocyanates are based on their electronic structure,[128] which can be represented by the structures (125)-(125c) (SCHEME 25).



X = Ph, CCl_3, CF_3

SCHEME 25.

The first type is 1,2-addition, taking place analogously as in isocyanates *via* attack of the nucleophilic centre of the substrate on the electrophilic carbon atom of the NCO group, [contributions of (125a) (major) and (125c) (minor)].

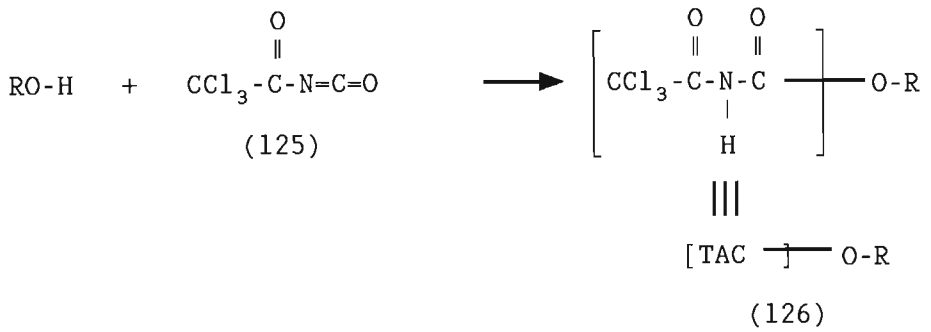
The second type, proper to acyl isocyanates, is 1,4-cycloaddition *via* structure (125b).

The reactivity of X-CONO increases with the electronegativity of X, and for X = CCl_3, [trichloroacetylisocyanate (TAI) (125)], the following relationship applies:

C_6H_5-CO-NCO < CCl_3-CO-NCO < CF_3-CO-NCO.

Thus, trichloroacetyl isocyanate derivatization of hydroxy groups, as an H^1 n.m.r. probe, was first introduced by Goodlet,[129] in 1965. He investigated the possibility of *in situ* acylations with diphenylketene, phenylisocyanate and

(TAI) (125), and found that TAI possesses all the properties necessary for an efficient acylation reagent. Thus, when TAI is applied to alcohols, the O*H* protons are converted to less mobile *imide* protons as indicated by the structure (126) (EQUATION 35). Their corresponding chemical shifts are then in the region of $\delta > 8$, where they are easily accessible for quantitative measurements.



EQUATION 35.

TAI-acylation induces characteristic acylation shifts, similar to acetylation but no group is introduced that would complicate the ^{1}H n.m.r. spectrum. The analytically significant information is the number and magnitude of the chemical shifts of the N*H* signals of the O-*TAC* (*O*-trichloro-acetyl carbamoyl) groups and the acylation-induced shifts of the adjacent α-CH protons.

Other workers have henceforth exploited and further developed the uses of TAI in the n.m.r. spectroscopy of amines and thiols,[130] and an extension to ^{13}C n.m.r. applications has also been reported.[131]

The literature has clearly demonstrated that the chemical shift differences of protons adjacent to the original OH, NH

and SH groups may be used to provide a wide range of structural information.[131] A further potential, although not predictable benefit, is that in many cases the addition of TAI leads to unmasking of overlapping resonances. In a general way, the resulting simplification of the spectra is similar to that obtained by the addition of lanthanide shift reagents without, however, the attendant loss of resolution.

Prior to this development, we had determined the *anti/syn* ratios by ^{1}H n.m.r. using Eu(FOD)$_3$ shift reagent where necessary and also by GC/MS. In those cases where ^{1}H n.m.r. was employed, the methylene signals between 5.5-6.5 ppm [H_A and H_B, (EQUATION 18)] were amenable to direct analysis in most cases studied.

However, we have found that these techniques, especially ^{1}H n.m.r. (even at 200 MHz) did not always yield a result because of poor separation of the diastereomeric signals. Furthermore, the most often used methylene signals were frequently "contaminated" with other signals which were inseparable from the ones of interest.

It was thus of interest to investigate whether a TAI-alcohol protocol could be developed to provide the required facile measurement of d.e.'s

We have noted that, on almost all the coupled acrylate systems investigated to date, such a TAI-derivatization method has proven successful and has greatly speeded up routine determination of d.e. values.[132]

2.3.1.1 EXPERIMENTAL PROCEDURE FOR TAI DERIVITIZATION.

Typically, the experimental procedure involved treatment of an n.m.r. sample [(±) 15-30 mg] with an excess (5-10%) of TAI. The sample tube is then shaken to ensure mixing and allowed a short time (about 5-10 minutes) to ensure complete reaction. Simple integration of the carbamate N*H* signals then provides the d.e. directly.

2.3.1.2 APPLICATION AND ADVANTAGES OF THE REAGENT.

FIGURE 17 shows the typical result of such a determination [for compound (127) at 3:2 diastereomer ratio], with the relevant N*H* signals distinctly appearing between 8.0 and 9.0 ppm.

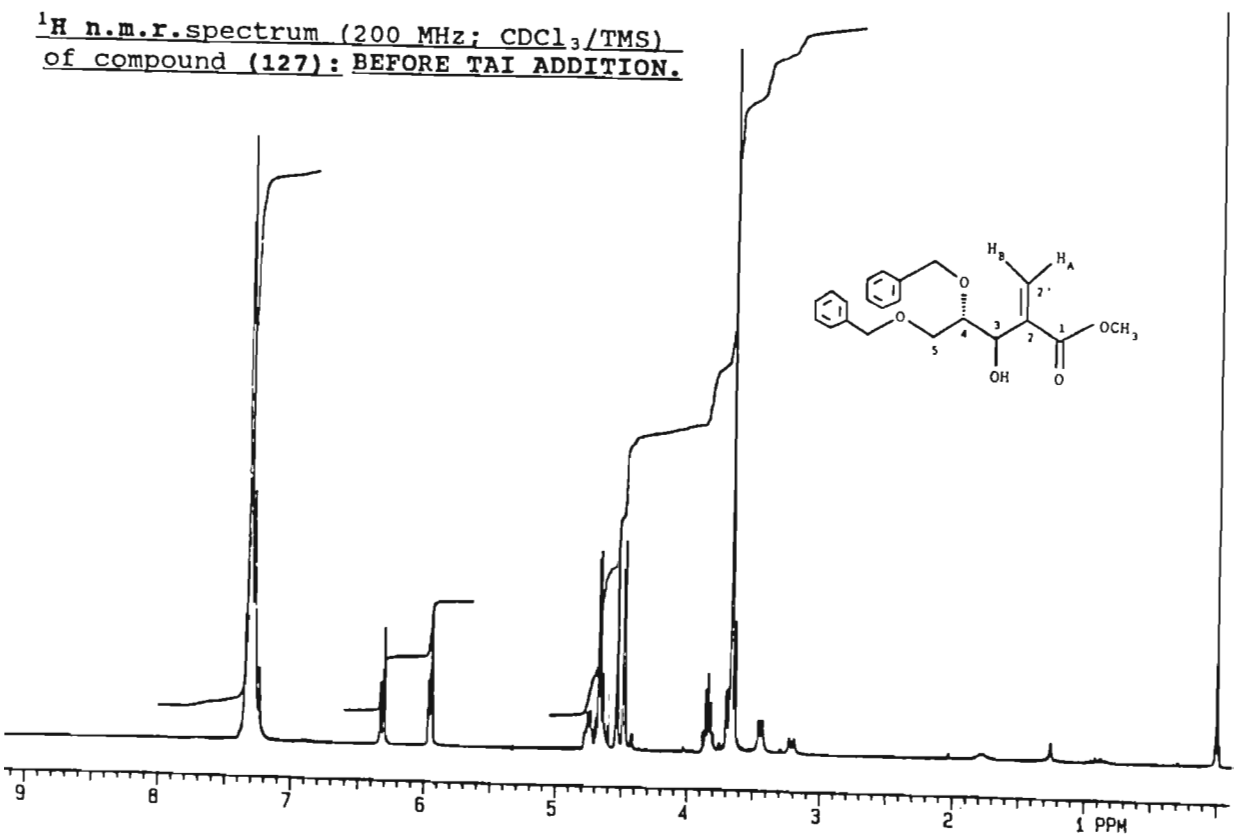


FIGURE 17

^{1}H n.m.r. spectrum (200 MHz; $CDCl_3$/TMS + *TAI*) of compound (127): AFTER TAI ADDITION, showing expanded *carbamate* region (inset).

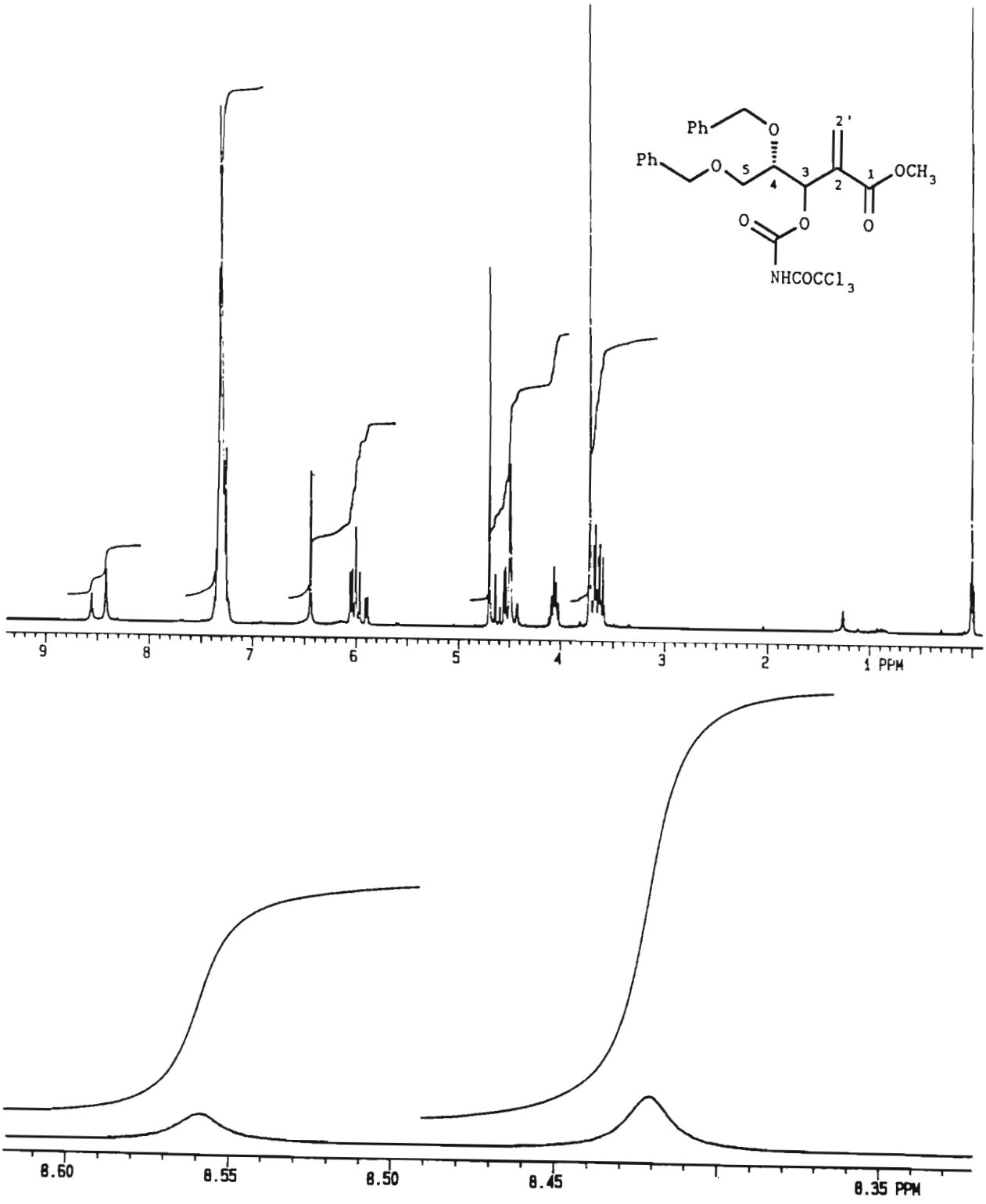


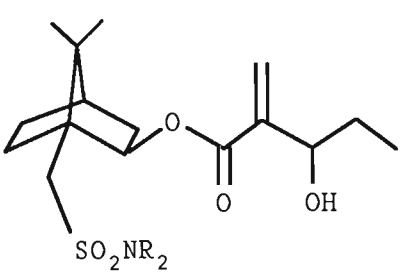
FIGURE 17

Amongst the advantages of this approach are the following important practical considerations:

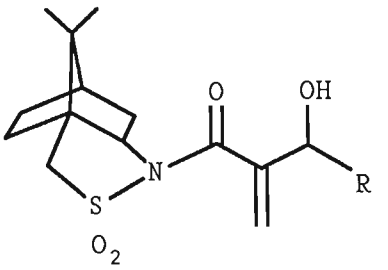
(1) The rapid, complete reaction with primary, secondary and tertiary hydroxy groups.
(2) The absence of the need for any special conditions, which allows the determination to be carried out *in situ*.
(3) The appearance of the carbamate N*H* singlets in the usually uncluttered 8.5-10 ppm region of the spectrum.
(4) Excess reagent can be added with impunity because TAI is devoid of protons and any excess does not measurably affect the chemical shift values.

Over the entire range of compounds investigated, it was pleasing to find a very good correspondence between the TAI determinations and independent corroberation by the more traditional means.

FIGURE 18 depicts some other systems that have been reported by Roos and Watson:[132]

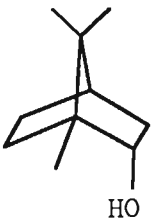


R = cyclo-C_6H_{11}, Bz

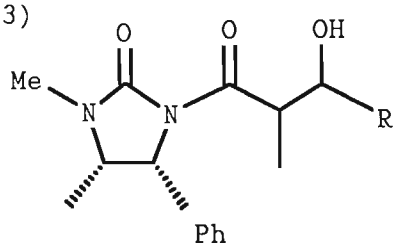


R = Et, Ph

(83)



(128)



R = CH_3, Ph, p-NO_2.C_6H_4, p-MeO.C_6H_4

(129)

FIGURE 18.

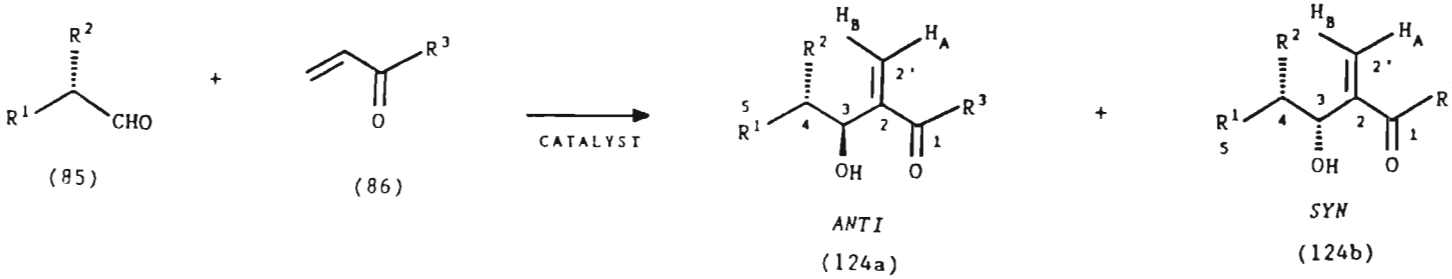
Although there will undoubtedly be exceptions, the above method offers a convenient course of action for d.e. measurement of diastereomeric alcohols, since it generallly requires no initial purification of the mixture and avoids the often complicating need to carry out separate derivatization reactions.

Possible side reactions due to substituent incompatibility and also solvent efffects have been mentioned in the literature. Thus, Roos and Watson[132] noted an enhanced resolution of the carbamate N*H* signals on changing the solvent from C_6D_6 to $CDCl_3$ in one case studied.

2.4 RESULTS AND DISCUSSION.

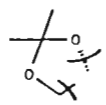
2.4.1 RESULTS.

The results of the diastereoselective coupling of the α-alkoxy/methyl aldehydes with activated vinyl systems (86) catalysed by DABCO (56) and/or (±)-3-quinuclidinol (72) to give compounds of general formula (124) (EQUATION 18) are presented in TABLE 5 below.



EQUATION 18.

TABLE 5: Asymmetric induction in the condensation between the α-alkoxy/methyl-substituted aldehydes and the activated vinyl systems.

ENTRY	ALDEHYDE	R^1	R^2	R^3	CATALYST[a] (MOLE %)	REACTION[c] TIME	COMPOUND	ANTI : SYN[d] RATIO	d.e. (%)	YIELD[e] (%)
1	11	Me	OBz	OMe	D (10)	14 d	130	60 : 40	20	68
2	104	Me	OMOM	OMe	D (10)	4 d	131	70 : 30	40	55
3	104	Me	OMOM	OMe	Q (10)	1.5 d	131	72 : 28	44	60
4	104	Me	OMOM	Me	D (10)	2.5 h	132	71 : 29	42	54
5	104	Me	OMOM	Me	Q (10)	<20 min	132	71 : 29	42	80
6	104	Me	OMOM	O'Bu	D (10)	1 mth	133	70 : 30	40	39
7	105	Me	OBOM	OMe	D (100)	6 d	134	70 : 30	40	41
8	105	Me	OBOM	Me	Q (10)	<1 h	135	77 : 23	54	79
9	105	Me	OBOM	O'Bu	Q (10)	1.3 mth	64	81 : 19	62	30
10	106	Ph	OMOM	OMe	D (10)	-	136	37 : 63	26	41
11	106	Ph	OMOM	OMe	D (100)	<3 d	136	44 : 56	12	27
12	106	Ph	OMOM	Me	D (10)	6 d	137	38 : 62	24	70
13	106	Ph	OMOM	Me	D (100)	3 d	137	42 : 58	16	52
14	107	^{i}Pr	OMOM	OMe	D (100)	>1.1 mth	138	51 : 49	2	24
15	108	^{i}Pr	OBOM	OMe	D (100)	23 d	139	41 : 59	18	68
16	108	^{i}Pr	OBOM	O'Bu	D (100)	1 mth	140	33 : 67	34	53
17	20			OMe	D (10)	>1.8 mth	141	69 : 31	38	62
18	20			OMe	Q (10)	>1.5 mth	141	75 : 25	50	39
19	20			O'Bu	D (10)	2.9 mth	66	66 : 34	32	61
20	115	CH_2OBz	OBz	OMe	D (10)	3.7 mth	-	-	-	-
21	115	CH_2OBz	OBz	OMe	Q (10)	1.2 mth	-	-	-	-
22	115	CH_2OBz	OBz	OMe	D (50)	<25 d	127	65 : 35	30	48
23	115	CH_2OBz	OBz	OMe	D (100)	<9 d	127	66 : 34	32	34
24	122	^{n}Pr	Me	OMe	D+Q (40)[h]	>2.2 mth	142	35 : 65	30	29

[a]Based on aldehyde.
D = DABCO (56)
Q = (±)-3-quinuclidinol (72).

[b]10 Mol% of DABCO, and 30 mol% of (±)-3-quinuclidinol subsequently added to speed up reaction rate.

[c]Reactions were monitored by H^1 n.m.r. by disappearance of the aldehyde peak.

[d]Diastereomeric ratios were determined by H^1 n.m.r., as discussed previously, except for ENTRIES 8 and 9, where GC/MS was employed. *Stereosubstructural assignments* will be detailed in *Section 2.4.3.4.*

[e]Overall yield of *anti/syn* mixtures after flash chromatography.[105]

2.4.2 RATE CONSIDERATIONS IN THE GENERAL BAYLIS-HILLMAN REACTION.

As with most useful methodologies, there are invariably some shortcomings. The Baylis-Hillman reaction, except with very carefully chosen component mixtures, is generally *slow*, and reaction times range from days to weeks for completion. This is in stark contrast to the claimed reaction time of seven days in the general method (patent[69]). Consequently, this problem has been addressed in a number of ways with varying degrees of generality associated with each of the solutions. These will be reviewed below.

2.4.2.1 PHYSICAL EFFECTS.

Ketones have remained inert as electrophiles in the Baylis-Hillman reaction. The only reports to date have been those of Hill and Isaacs,[84,133] where pressures of the order of up to 12 kbar have resulted in dramatic rate acceleration and also for the limited use of ketones and terminally substituted vinyl components, i.e., crotyl derivatives. Furthermore, simpler tertiary amines such as triethylamine have also proven effective. Nevertheless, this is still the only successful report of a solution to what may be termed the "crotyl" problem.

Recent observations, and also present investigations, as yet unpublished, by Roos[134] involves the use of ultra sound in attempts to achieve useful rate enhancements.

2.4.2.2 COMPONENT REACTIVITIES.

These solutions tend to be very specific and simply reflect the anticipated order of reactivity dependent on the nucleophilic vinyl and electrophilic carbonyl components, for example, use of diethyl ketomalonate as "electrophile", as shown by Basavaiah and Gowriswari,[135] or use of methyl vinyl ketone[70] as "nucleophile".

Emslie and co-workers[136] have recently shown that the choice of acrylic ester has a profound effect on reaction rate and also the reaction pathway.

Basavaiah and Sarma[137] have recently demonstrated a moderate effect on rate by the use of terminal hydroxyalkyl acrylates, exploiting the earlier idea of a possible hydrogen-bonded species by Kaye and co-workers.[83] This is in

line with rate enhancement attempts, *via* the addition of alcohols,[83] where, attention was focussed on the mechanistic step involving amine liberation for further reaction.

More recently, Bode and Kaye[82] have shown that reaction rate is sensitive to variation of both the aldehyde substituent (R^1), and the alkyl substituent (R^2) (SCHEME 11) (CHAPTER 1).

2.4.2.3 CATALYSTS.

Much of the effort here has been centred on the proposed reaction step[82,139] that releases the amine for further reaction. Drewes *et al.*[138] have also shown that (±)-3-quiniclidinol (72) is a superior catalyst compared with DABCO (56), and thus concluded that the free hydroxyl group is important in the reaction so that the previously proposed hydrogen-bonded stabilisation[83] does occur. The latter speculation becomes important when it was observed that use of heterocyclic aldehydes showed great rate enhancements. This same observation has also been noted by Hoffman and Rabe[139] who support the idea that basic heteroatoms could aid proton migration. This hydrogen-bonded model has been supported by the kinetic and mechanistic study of Bode and Kaye.[82]

The fairly obvious relationship between catalyst concentration and reaction rate was recently reported by Basaviah *et al.*.[89] We[140] have thus also noted that, whilst the more traditional reaction component mixtures simply respond by reacting faster, some of the less reactive components only start to show reactivity after a certain catalyst concentration is reached. It is reasonable to state that they would react at low catalyst concentrations, but at

such a slow reaction rate that it is not observable within a reasonable period.

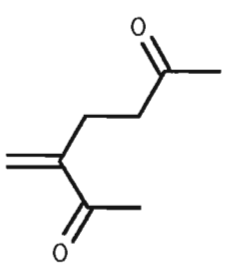
2.4.3 DISCUSSION.

2.4.3.1 REACTION RATE AND YIELDS.

It should be noted that at the time of commencement of this investigation, the amount of catalyst used was the standard 10 mol%, based on the aldehyde. This ratio was subsequently stepped up to molar equivalents after the recent report by Basavaiah *et al.*.[89]

With respect to reaction rate (TABLE 5), it is evident that these reactions are generally slow, ranging from days up to months to reach completion. It is also evident that catalyst Q and the methyl vinyl ketone function are important determinants of reaction rate whilst not affecting the stereoselectivity (ENTRIES 2, 3, 4 and 5).

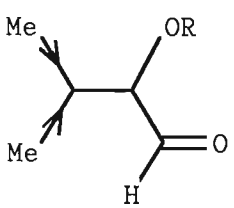
In those cases where methyl vinyl ketone was the activated vinyl component, the amine-catalysed Michael-type dimerization product (143) was also isolated from the reaction mixture during purification.



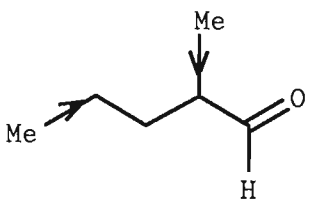
(143)

This obversation is in accordance with earlier reports by Amri and Villiéras.[141] If however, the reactants are diluted[142] with THF, then only the required allylic alcohols are obtained.

With respect to the O-protected aldehydes, (ENTRIES 1-9), an increase in steric hindrance of the protective groups R^2 and also the ester group R^3, lead to longer reaction times. This also pertains to increasing the steric requirements of the aliphatic residue R^1, as in the case of the isopropyl [(107)and (108)] and the α,β-dialkoxy aldehydes [(20) and (115)] (ENTRIES 14-23). The much slower reactivity of the aldehydes [(107) and (108)] (and even the simple methyl substituted aldehyde (122)) can possibly be attributed to the inductive effects of the methyl groups (or even due to steric effects) which consequently lead to deactivation of the electrophilic carbonyl carbon (FIGURE 19).



(107), (108)



(122)

FIGURE 19.

The change in R^1 from Me to CH_2OBz results in no reaction even after about four months (ENTRIES 1 and 20), in contrast to the isoproylidene derivative (20) where reaction was observed. However, on changing R^2 from O-alkyl to alkyl (R^2 = Me) (ENTRY 24) the reaction is slow even at 100 mol% of catalyst.

The yields, although no optimisation was carried out, range from poor to good, and are, in general, within the synthetically useful range.

2.4.3.2 DIASTEREOSELECTIVITY.

With regard to the stereochemical results (TABLE 5), the following features can be observed:

(1) The *anti/syn* ratios are unaffected by the choice of catalyst, (D or Q), or even the amount of catalyst, (10, 50, 100 mol%, ENTRIES 2, 3, 4, 5, 22, 23), except for ENTRIES 10-14, 17 and 18, where a slight improvement was observed.

(2) Due to the absence of the "more usual" coordinating metal counter cation under these reaction conditions, one would predict overall *anti*-selectivity in all cases, stereoselectivity thus being dictated by steric and/or electronic effects. However, inspection of the above results indicate overall *syn*-selectivity for the aldehydes [(108), (106) and (122)], increasing in the order Ph, ^{n}Pr, ^{i}Pr for the aliphatic moiety R^{1}.

(3) With respect to variations in R^{3}, the changeover from an acrylate ester to a vinyl ketone system does not affect the *intrinsic* diastereoselectivity, i.e., *anti* or *syn*. However, it does improve the *anti* selectivity in ENTRIES 7 and 8.

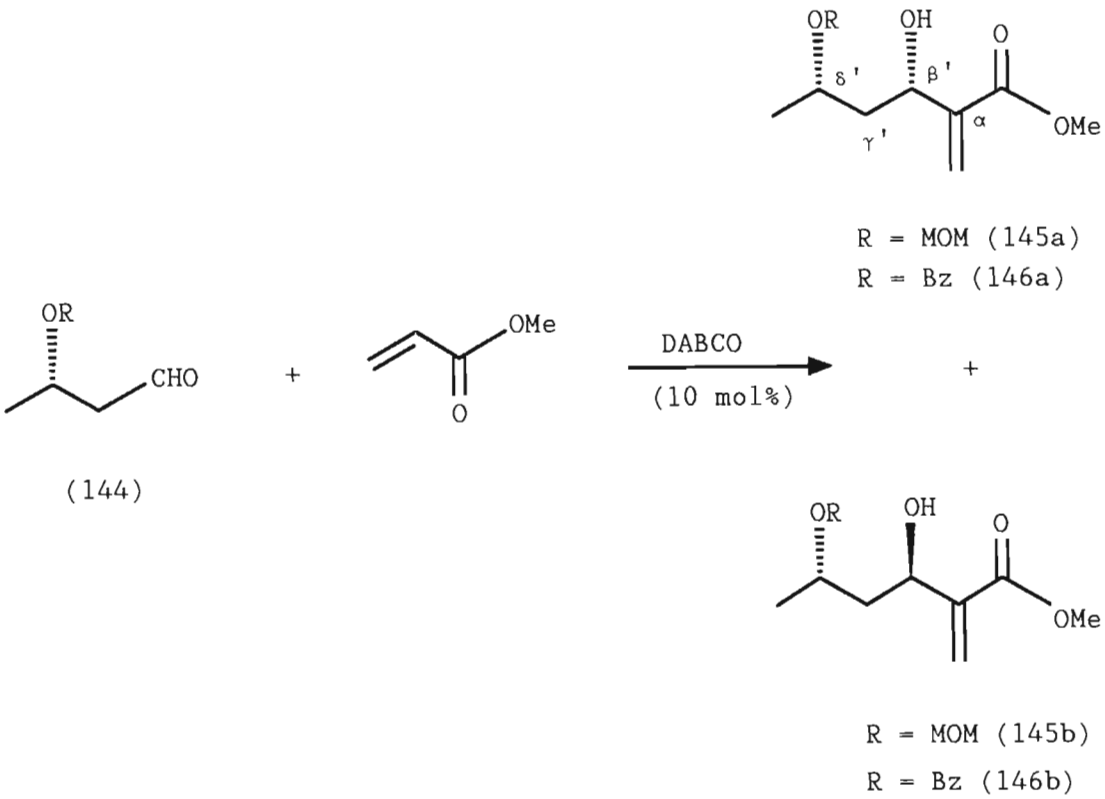
An increase in steric bulk from the methyl to the *tert*-butyl acrylate does not lead to a reversal of the overall diastereoselectivity (*anti* or *syn*) (ENTRIES 2, 3, 6; 7, 9; 15, 16 and 17, 18, 19). However, it does improve the *intrinsic* selectivity for aldehyde (105) (ENTRIES 7 and 9), aldehyde (108) (ENTRIES 15 and 16), but decreases the selectivity for aldehyde (20) (ENTRIES

17, 18 and 19).

(4) With variations in the protecting group R^2, it is evident that the overall diastereoselectivity, with R^1 constant (and/or variations in R^3), remains unaffected (ENTRIES 1, 2-9 and 15, 16). However, in the case of the aldehyde (107) (ENTRY 14), the stereochemical outcome is virtually stereorandom (about 1:1 *anti*:*syn*) and also, in this instance, changing from the *OMOM* to the "bulkier" *OBOM*-protecting group improves the diastereoselectivity and, at the same time, the *intrinsic* selectivity, (taking the diastereoselectivity as *anti*), is reversed to *syn* (ENTRIES 14, 15 and 14, 16).

In those cases where *anti* selectivity is observed, the *OMOM* protecting group results in improved selectivity compared with the O-*benzyl* protecting group (ENTRIES 1, 3 and 3, 23).

These results are in contrast with the results of recent studies[143] on the use of chiral α-unsubstituted-β-alkoxy aldehydes (144) in the Baylis-Hillman reaction (EQUATION 36).



EQUATION 36.

The following results were obtained[143] (TABLE 6).

TABLE 6: Synthesis of α(-δ'-alkoxy-β'-hydroxyalkyl) acrylates.

R	COMPOUND	% d.e.
CH_2OCH_3	145	86
CH_2Ph	146	51

It is evident that the *OMOM* protecting group gave better diastereoselectivity as compared with the *O-benzyl* protecting group. *Syn* selectivity was rationalised by extension of Cram's "cyclic" model[25,26] for asymmetric induction, where intramolecular chelation between the methylene group of the acetal and the carbonyl oxygen, to form a six-membered ring, was proposed[143] (FIGURE 20).

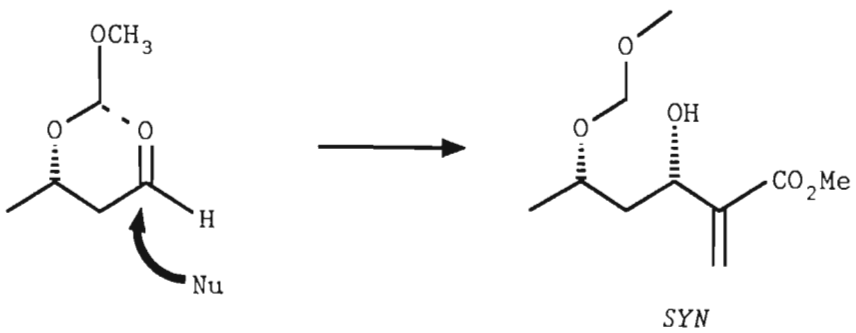
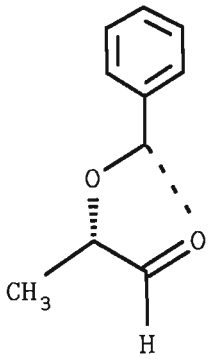


FIGURE 20.

If the above transition state is operating in the case of our α-chiral substituted aldehydes, one can predict better *anti* diastereoface selectivity for the *O-benzyl* protected aldehyde (11) due to the electron donating influence of the benzene ring and thus disfavouring this "chelated" transition state (FIGURE 21).



(11)

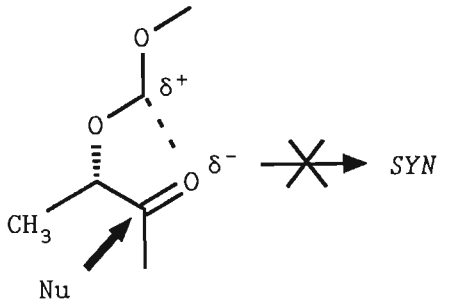


FIGURE 21.

Our results imply that the *OMOM* protecting group is "larger" than the O-*benzyl* protecting group with respect to relative steric sizes.

It is also evident that the *OBOM* protecting group gives equivalent and superior results as compared with the *OMOM* group (ENTRIES 3, 7; 3, 8 and 3, 9) and the O-*benzyl* group (ENTRIES 1, 7; 1, 8; 1, 9; 23, 7; 23, 8 and 23, 9).

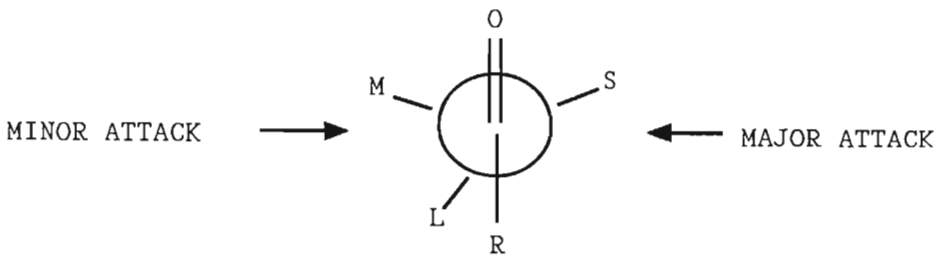
In those cases where *syn* selectivity was observed, the degree of selectivity beween *OMOM* and *OBOM* are similar (ENTRIES 13, 15; 10, 16; 10, 24 and 16, 24). However, the *OBOM* protecting group results in the best *intrinsic* diastereoselectivity as compared with the other protecting groups (ENTRIES 9 and 16).

(5) With variations in the aliphatic moiety R^1, *anti* diastereoselectivity decreases on moving from the simple Me to the isopropylidene and the CH_2OCH_2Ph groups to the stage where, with the Ph, ^{i}Pr and ^{n}Pr groups, a *reversal* of diastereoselectivity to the *syn* isomer is observed (ENTRIES 9, 18, 23, 11, 15 and 24). However,

taking the best results (ENTRIES 10, 16 and 24), the observed *syn* selectivity is virtually comparable (about 30% d.e.).

Since these reactions were carried out under *metal-free non-coordination* reaction conditions, the Cram chelation ("cyclic") model,[25,26] which is frequently applied to rationalize *syn* diastereoselectivity, is not operative in these cases.

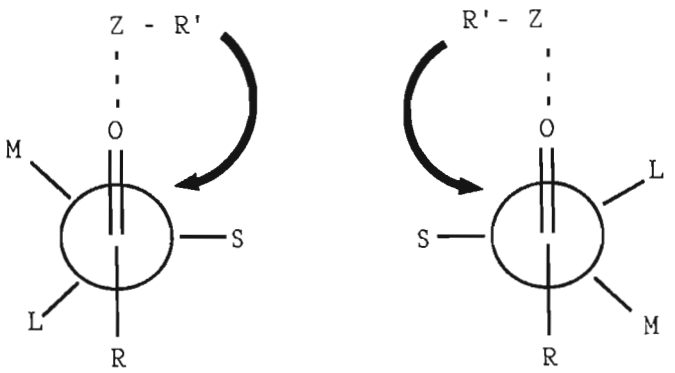
The original formulation of Cram's model was "...that diastereomer will predominate which would be formed by the approach of the entering group from the less hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least hindered bulky groups attached to the asymmetric centre".[24] This statement implies a one-conformer model (*1a*), with major and minor diastereomers resulting from attack on the less and more hindered carbonyl faces.



(1a)

However, in a later paper on the subject, Cram and Kopecky presented a Newman projection of the conformation that is assumed to lead to the major diastereomer [formula (*1b*]).[25] This formulation of Cram's rule implys a two-conformer model [(*1b*) and (*1c*)] (FIGURE 22), in which the smallest ligand attached to the stereocentre is approximately perpendicular

to the plane of the carbonyl group and attack of the nucleophile occurs from this face.



(1b) *(1c)*

FIGURE 22.

Thus, stereodifferentiation would result from differential gauche interactions in (*1b*) and (*1c*).

It was assumed that the cation of the reagent (Li^+ or Mg^+) coordinates with the oxygen, which "therefore becomes effectively the bulkiest group in the molecule and tends to orientate itself between the two least bulky groups attached to the adjacent asymmetric carbon atom".[24,25]

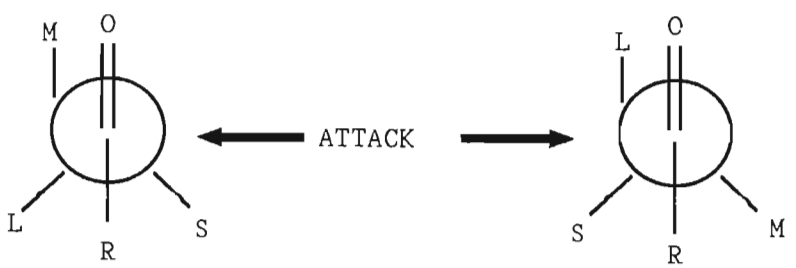
Subsequent discussions of Cram's rule have not been consistent in treating it either as a one-conformer or two-conformer model. For example, whereas Morrison and Mosher[7] and Eliel[144] have used the two-conformer models (*1b*) and (*1c*) in their reviews, Karabatsos[29] and Anh[33] have criticized the rule on the basis of the one-conformer model (*1a*). In his important paper on the subject,[30] Felkin illustrated both the one-conformer and two-conformer models.

In 1967, Karabatsos[29] pointed out certain limitations of

Cram's model and proposed a model based on the known minimum energy conformations of aldehydes and ketones. The model is based on the following assumptions:

(1) Little bond making and bond breaking occurs at the transition states so that the arrangement of groups of the asymmetric carbon is similar to that about sp^2-sp^3 carbon-carbon bonds, that is, one ligand on the α-carbon is eclipsed with the C=O bond.

(2) The two low energy diastereomeric transition states that control product stereospecifity have the smallest group of the asymmetric carbon atom closest to the incoming nucleophile (FIGURE 23).



MAJOR
(2a)

MINOR
(2b)

FIGURE 23.

(3) The diastereomeric ratio (qualitative prediction) is then evaluated from the relative magnitudes of the carbonyl-eclipsed group interactions, that is, O↔M vs O↔L).

Thus, the major and minor products would arise from attack on the less hindered face of conformers of the aldehyde or ketone, in which the medium and large groups are eclipsed with the C-O bond [*(2a)* and *(2b)*]. The relative energies of these conformers are often known from other physical

measurements.

Cherest, Felkin and Prudent[30] noted that neither the Cram[24-26] nor the Karabatsos[29] models are particularly applicable to cyclohexanones and that neither model accounts for the effect of the carbonyl ligand R on the magnitude of the stereoselectivity. These workers proposed a third model which assumes that the dominant interacton is that between the incoming nucleophile and the largest group attached to the stereocentre, that is, that the nucleophile attacks *anti*-periplanar to the large group as shown in (*3a*) and (*3b*) (FIGURE 24).

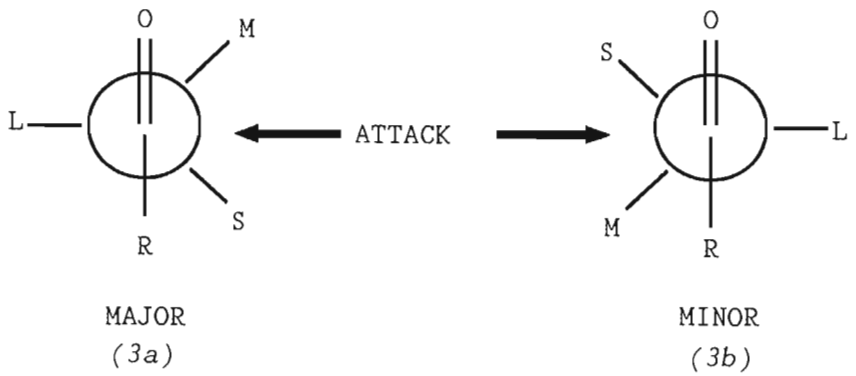


FIGURE 24.

In the Felkin model,[30] interaction of the carbonyl oxygen with the medium and small ligands is ignored and stereo-differentiation results from differences in the gauche interactions of R with these groups. The necessity of making this assumption, particularly for aldehydes, is an obvious weakness of the Felkin model. Nevertheless, it is assumed that the R↔M interaction is greater than the R↔S interaction and that conformation (*3a*) therefore leads to the major product.

Anh and Eisenstein[33] evaluated the Cram,[24-26] Karabatsos[29] and Felkin[30] models by *ab initio* calculation of hypothetical transition states. It was then noted that the Felkin conformers (*3a*) and (*3b*) were found to be significantly lower in energy than the Cram conformers (*1a-c*), or the Karabatsos conformers (*2a*) and (*2b*). Although the Ahn-Eisentein paper[33] discusses Cram's model in terms of the one-conformer model (*1a*), it may be seen from Figure 2 in that paper that conformers (*1b*) and (*1c*) are both calculated to be of higher energy than that of (*1a*).

Before their contributions are outlined, a brief review of the "Burgi-Dunitz trajectory"[145-147] is relevant at this stage.

In their experimental and theoretical studies on the stereochemistry of reaction paths at carbonyl centres, viz., nucleophilic addition to the carbonyl group, Burgi and Dunitz[145-147] found that the reaction paths by different methods for different nucleophiles showed striking similarities that appeared to be characteristic for the reaction type. It was shown from structural correlations that the path of approach of a nucleophile to the carbonyl group with which it can react is defined by a displacement (Δ) of the carbon atom out of the plane defined by its three-bonded atoms (two substituents R and R^1, and the carbonyl oxygen atom). The out-of-plane displacement (Δ) increases as the Nu....C-atom distance decreases, following a logarithmic relationship (FIGURE 25).

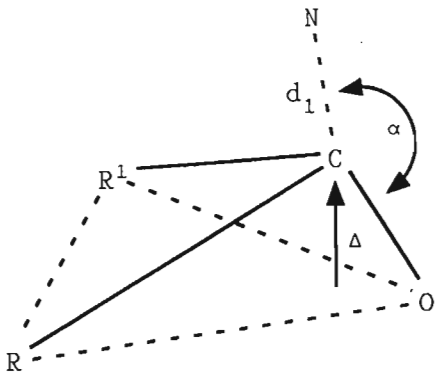


FIGURE 25.

Thus it has been shown, that for a tertiary amino group, for d_1 < 3 Å, the approach path of the nucleophile lies in a plane bisecting the RCR^1 angle and is virtually along a straight line inclined at an angle of about 107° to the C-O bond.

Thus, Anh and Eisenstein[33] made the following further contributions:

(1) It was pointed out that, by incorporation of the Burgi-Dunitz trajectory, as shown in (*4a*) and (*4b*) (FIGURE 26), the observed stereoselectivity can be explained without the necessity of assumptions relating to the relative magnitudes of the O↔M and R↔M interactions.

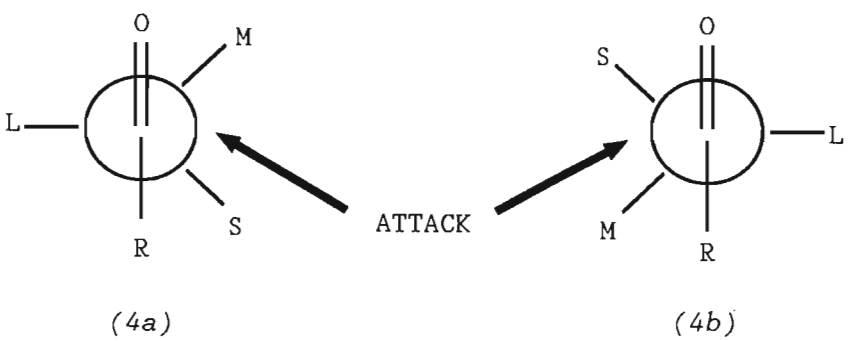


FIGURE 26.

It is implicitly assumed that conformations (*4a*) and (*4b*) are of comparable intrinsic energy and that stereodifferentiation arises from differential interactions of the attacking nucleophile with the small and medium ligands.

(2) It was proposed, on the basis of frontier molecular orbital arguments, that the ligand with the lowest σ* orbital, rather than the sterically most demanding group, is perpendicular to the carbonyl plane and *anti* to the attacking nucleophile. By this criterion, O-R will always be "larger" than *alkyl* or *aryl*.

In terms of the Karabatsos model,[29] our observed diastereomer ratios, can, from a qualitative point of view, be rationalised as follows:

The *anti* diastereoselectivity for aldehydes [(11), (104), (105), (20) and (115)], where the aliphaic moiety R^1 = CH_3, CH_2O^iPr and CH_2OBz respectively, is the major product predicted by the Karabatsos conformer (*2a'*) in which the medium group R^1 and the large group R^2 are eclipsed with the C-O bond, where the $R^1 \leftrightarrow O$ interaction is favoured over the $R^2 \leftrightarrow O$ interaction (FIGURE 27).

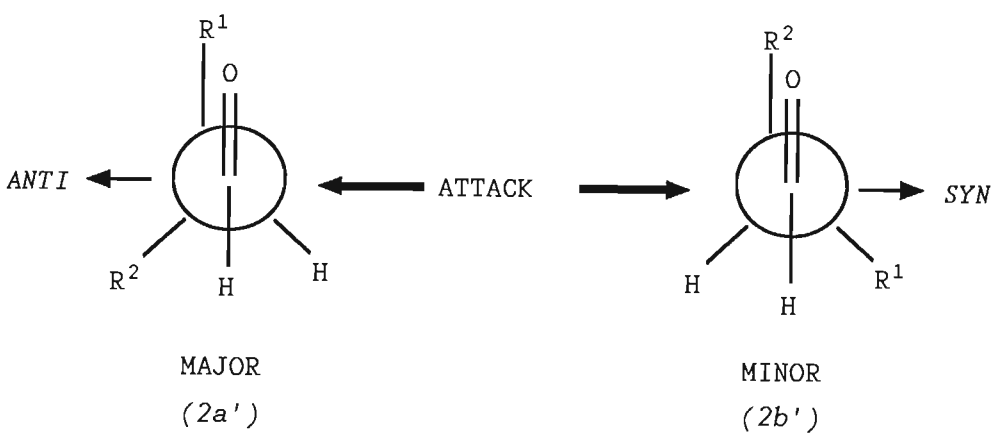


FIGURE 27.

In contrast, the predominance of *syn* selectivity for the aldehydes [(106), (108) and (122]), where the aliphatic moiety R^1 = Ph, ^{i}Pr and ^{n}Pr respectively, can be explained if one evaluates the major conformer (*2b'*) where the medium group (R^2= OMOM, OBOM and Me) and the large group (R^1 = Ph, ^{i}Pr and ^{n}Pr) are eclipsed with the C-O bond (FIGURE 28).

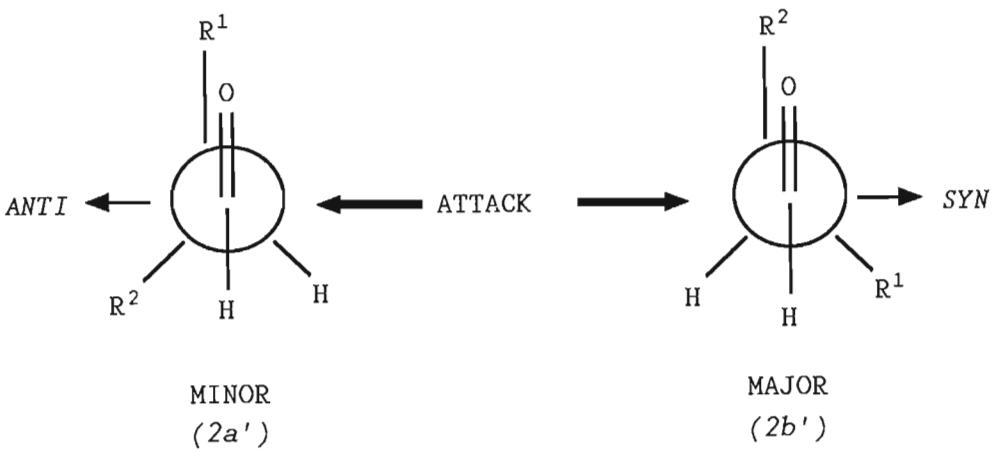


FIGURE 28.

Thus, in this instance, the aliphatic moiety R^1 = phenyl/isopropyl seems to take the role of the "large" group, that is, Ph and ^{i}Pr are considered larger than OMOM and OBOM for the aldehydes (106) and (108) respectively.

On the basis of the observation that no significant difference exists between the steric discrimination of OMOM and OBOM (ENTRIES 2 and 7), the stereorandom result obtained for aldehyde (107) (ENTRY 14) is anomalous when compared to the observed *syn* diastereoselectivity with the aldehyde (108) (ENTRIES 15 and 16), suggesting that reaction proceeds equally through both conformers in FIGURE 27.

It is also evident that the observed *syn* selectivity increases in the order for R^1 = ^{i}Pr, Ph, ^{n}Pr (ENTRIES 15, 10 and 24). These results do not follow the expected trend. A

phenyl group is commonly considered to be "larger" than isopropyl.[148] Inspection of the major conformer (FIGURE 28) would imply that, for R^1 = ^{i}Pr, Ph, and R^2 = OMOM, the Me↔O=C interaction, when R^1 = ^{n}Pr, is favoured over the R^2↔O=C interaction as expected. However, this conformer cannot be used to evaluate whether the above observed order in the case of ^{i}Pr and Ph is justified. Thus, on the contrary, the observed *anti* selectivity increases in the order ^{n}Pr, Ph, ^{i}Pr. Inspection of the minor conformer above (FIGURE 28) would imply that the ^{n}Pr↔O > Ph↔O > ^{i}Pr↔O interactions for the above order, which is obviously unexpected. In accordance with our observed results, the major conformer, (FIGURE 28), predominates, thus giving rise to the *syn* isomer.

In terms of the "Felkin-Anh" model,[30,33] the major (*anti*) diastereomer for aldehydes [(11), (104), (105), (20) and (115)], where R^1 = CH_3, $CH_2O^{i}Pr$, CH_2OBz, is that product predicted by the "Felkin-Anh" model if one assumes that the alkoxy group plays the role of "large" group (FIGURE 29).

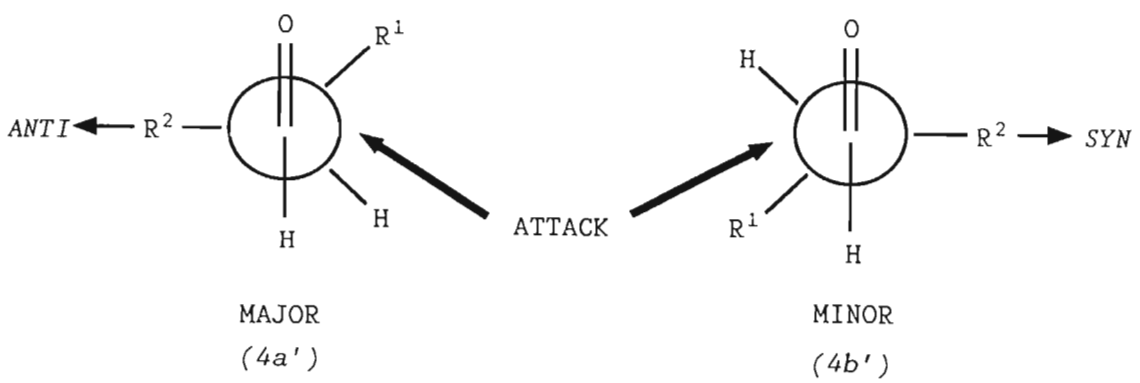


FIGURE 29.

This is to be expected on the basis of the Anh-Eisenstein[33] hypothesis, as carbon-heteroatom bonds (C-O) have significantly lower σ*-orbital energies than carbon-carbon (C-C) bonds.

With respect to the relative degree of *anti* diastereofacial selectivity, the observed results indicate increasing *anti* selectivity in the order for $R^1 = CH_3$ (R^2 = *O*-Bz), CH_2OBz (R^2 = *O*Bz), CH_3 (R^2 = *O*MOM, *O*BOM), CH_2O^iPrO (R^2 = O^iPrO), for the aldehydes [(11), (115), (104), (105) and (20)] (ENTRIES 1, 23, 2, 7 and 18).

As the size of R^1 increases from CH_3 to CH_2OBz (or CH_2O^iPrO) for aldehydes [(11) and (115)] (and 20), diastereoface selection increases as expected, from a comparison of the interactions between the attacking nucleophile (which is the same in these cases) and R^1 (on the "Burgi-Dunitz trajectory").

Furthermore, variation of the protecting group R^2 from *OBz* [aldehydes (11) and (115)] to *OMOM* [aldehyde (104)], [or to *OBOM*, aldehyde (105)], and/or to O^iPrO [aldehyde (20)], results in increasing *anti* diastereoselectivity. Heathcock *et al.*[149] also found that diastereoface selection was increased by using protecting groups containing an acetal moiety such as the methoxymethyl (MOM) group. This behaviour has been explained on the basis of the reduced basicity of the α-oxygen, caused by the inductive effect of the second oxygen, which disfavours a chelated transition state. Our results appear to agree with the latter interpretation.

The above results (ENTRIES 2, 7) also indicate that the *OMOM* and *OBOM* protecting groups do not exhibit any diastereofacial preference. It is only when the more sterically demanding ^{t}Bu-acrylate is employed that discrimination is evident (ENTRIES 7, 9).

Regarding the stereochemical results for the aldehydes (106) and (108) (ENTRIES 10-13, 15 and 16), application of the "Felkin-Anh"[30,33] model predicts the *wrong* diastereomer where R^1 = Ph and ^iPr respectively.

On the basis of the Anh-Eisenstein hypothesis,[33] the alkoxy group (OR^2 = OMOM, OBOM) would be placed *anti* to the attacking nucleophile, as carbon-heteroatom bonds have significantly lower σ*-orbital energies than carbon-carbon bonds (C-O < C_{sp^2}=C_{sp^2}; C-O < C_{sp^3}-C_{sp^3}). Thus, by this model, the major diastereomer should be *anti* in each case [conformer (*4a'*) (FIGURE 29)].

The latter results can be rationalised by Felkin transition states, if one evaluates a *four-conformer equilibrium*, as depicted in FIGURE 30.

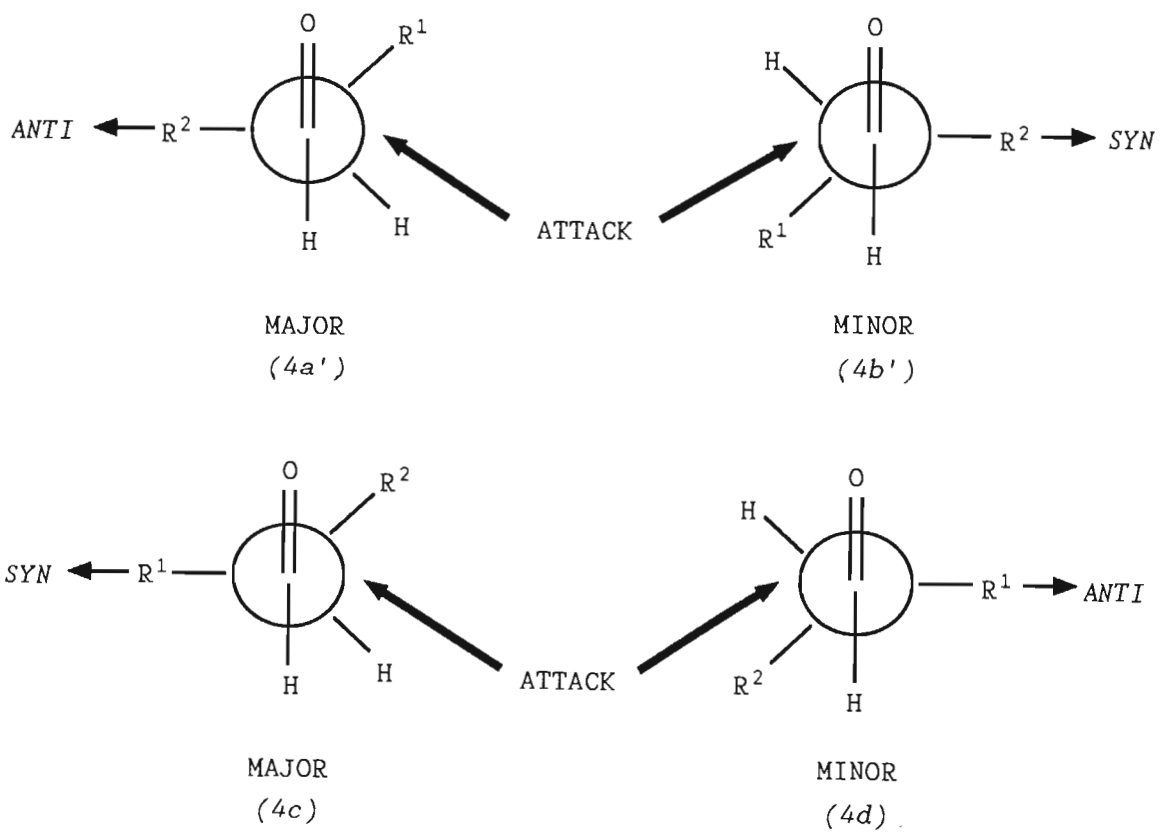


FIGURE 30.

We propose that our results indicate that the Anh-Eisenstein[33] hypothesis is only *partly* applicable in these cases. Thus, when using the "Felkin-Anh"[30,33] model for 1,2-asymmetric induction, the choice of "large" ligand (group) should consider both the natures of the bonds from the chiral centre to the three ligands (groups) as well as the steric bulk of the three ligands (groups). In nucleophilic additions to the aldehydes [(11), (104), (105), (20) and (115)], the alkoxy group R^2 takes the role of "large" group when pitted against CH_3, CH_2O^iPr or CH_2OBz. As a result of preferred reaction through the conformer (*4a'*), the major products are the *anti* diastereomers. The minor products (*syn*) arise presumably from addition to conformer (*4b'*).

With aldehydes (106) and (108) (ENTRIES 10-13, 15 and 16), conformers (*4c*) and (*4d*) are more important, in which the bulky phenyl and isopropyl groups play the role of the "large" group. These results can be rationalised on the basis of the following two conclusions:

(1) The phenyl group represents an increased steric effect over the methyl group of the lactaldehyde series.
(2) The σ*-orbital energies of the sp^2 carbons of the phenyl group are lower than those of the sp^3 carbons of the methyl group. This allows the phenyl substituent to compete more effectively with the alkoxy group in terms of both steric (Felkin[30] model) and electronic (Anh-Eisenstein[33] "model") factors.

In these cases, reaction appears to proceed about two thirds through conformer (*4c*) and one third through conformer (*4a*) (ENTRIES 10 and 15).

As the bulk of R^3 increases from Me to ^{t}Bu for the aldehyde (108), diastereofacial selectivity increases (ENTRIES 15 and 16) due to increasing steric interactions between the attacking nucleophile and the R^2 group in conformation (*4c*).

These results would appear to imply that the Ph group is *larger* than the OMOM group and also that ^{i}Pr is *larger* than the OBOM group. With these considerations in mind [together with the observation that variation of R^2 from *OMOM* to *OBOM* does not enhance the streoselectivity (ENTRIES 2 and 7)], the results observed for aldehyde (107) is thus an anomoly. Reaction through conformers (*4c*) and (*4d*), in this instance, presumably gives rise to a *syn/anti* ratio of less than unity (ENTRY 14).

By contrast, it is also evident that although the phenyl group is larger than the isopropyl group, the results indicate that phenyl gives a slightly lower *anti*/syn ratio than does isopropyl (ENTRIES 10 and 15), if one ignores the effects of R^2, which do not appear to be significant at all (as based on the earlier results in TABLE 5). In addition, the σ^* orbital energies of a C_{sp^2}-C_{sp^3} bond is lower than that of a C_{sp^3}-C_{sp^3} bond.[150] With this aldehyde (106), we propose that the "unfavourable" interactions between the incoming nucleophile and the phenyl group ($Nu^{-}\leftrightarrow{}^{-}Ph$) in conformation (*4a'*) (which gives rise to the minor *anti* product), leads to predominance of reaction through conformer (*4c*) as compared with the corresonding nucleophile-isopropyl group interactions ($Nu^{-}\leftrightarrow{}^{i}Pr$) in conformation (*4a'*), for aldehyde (107) or (108) (FIGURE 31). In other words, the relative conformer populations of (*4c*) is greater for aldehyde (106) than for (107) so that higher *syn* selectivity is observed for (106) than for (107) (ENTRIES 10, 14 and 15).

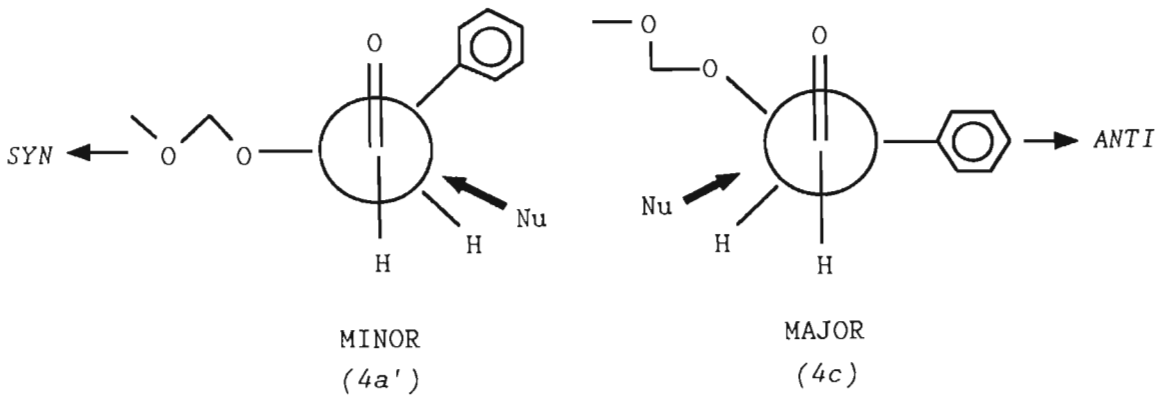


FIGURE 31.

At this stage, it is interesting to note that the only reported investigation of the use of chiral α-substituted aldehydes in the Baylis-Hillman reaction is a recent report by Isaacs and co-workers,[85] describing their attempts at asymmetric induction. Under conditions of *high pressure*, they obtained the following results (TABLE 7).

TABLE 7: Diastereomeric excess in reactions between acrylic compounds and chiral aldehydes.

acrylic cmpd.	aldehyde r*	p/kbar	T/°C	t/h	Yield/%	de/%
acrylonitrile	(R)-myrtenal 1:4	5.5	23	42	42	16
acrylonitrile	isopropylidene (R)-glyceraldehyde	4	25	21	47	23
ethyl acrylate	isopropylidene (R)-glyceraldehyde	4	25	21	39	-

It is evident that the results obtained are mediocre. Furthermore, no induction was observed under conditions of atmospheric pressure.

Our results indicate a much higher d.e. of 32-50% for the methyl acrylate/(R)-isopropylideneglyceraldehyde coupling product (141) (TABLE 5) at *atmospheric* pressure.

Finally, with the simply substituted α-methyl aldehyde (122), where both non-hydrogen substituents are carbon, that is, absence of any major electronic contribution, application of the "Felkin-Anh"[30,33] model predicts the observed stereoselectivity. Thus, the *n*-propyl obviously plays the role of "large" group and reaction proceeds through the conformers (*4c'*) and (*4d'*) (FIGURE 32).

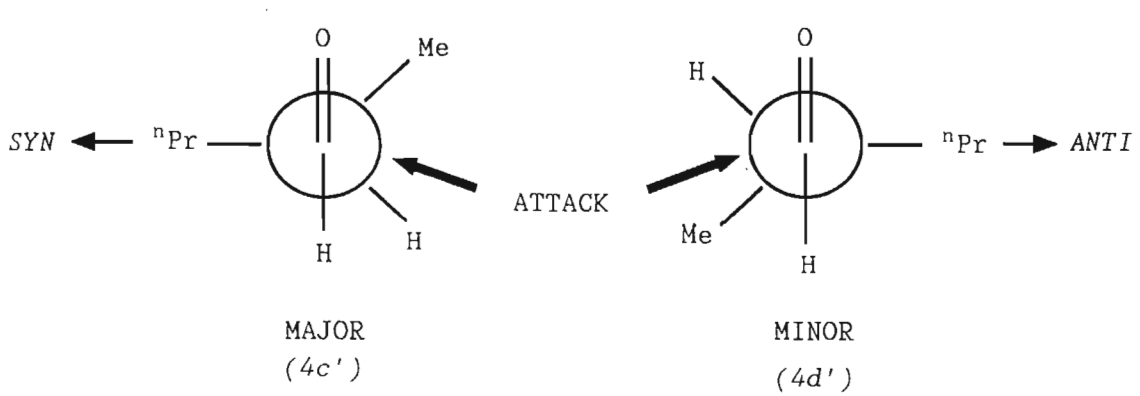
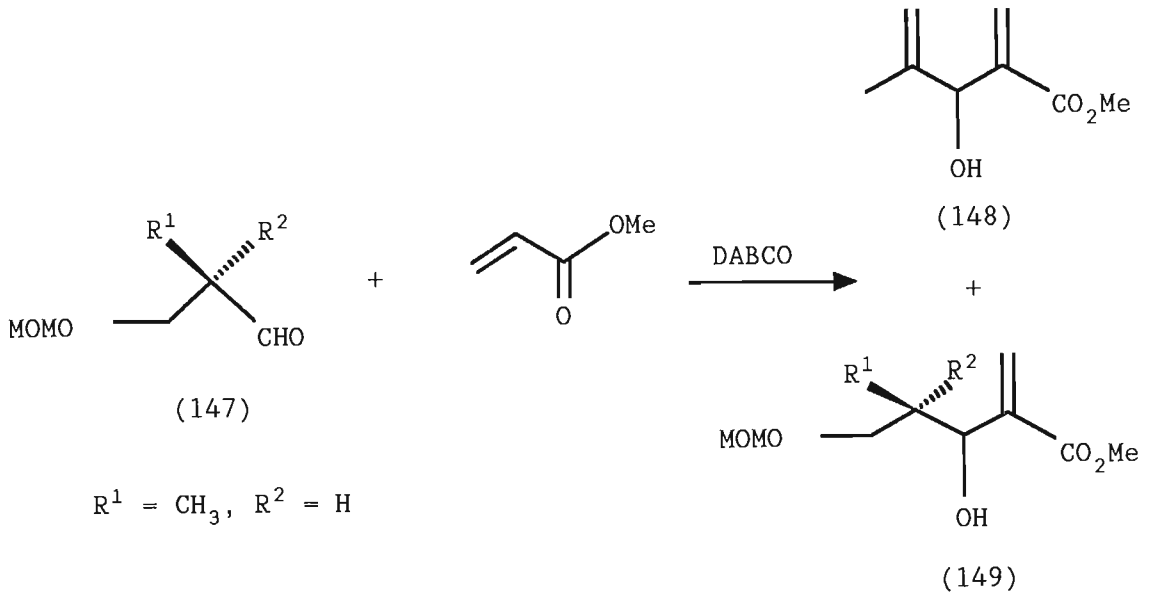


FIGURE 32.

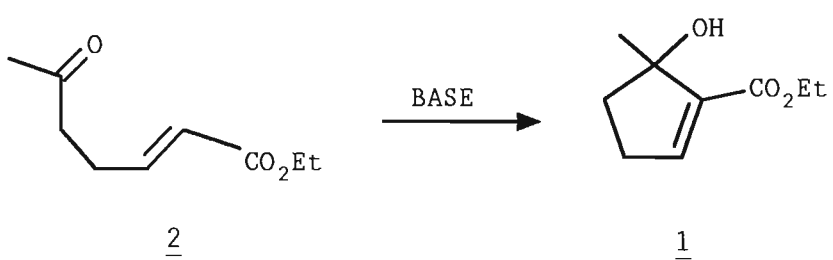
It should also be noted that recent studies[143] on the reaction of α-substituted, β-alkoxy aldehydes (147) with methyl acrylate afforded the 3-hydroxy dimethylene ester (148) in quantitative yield, with only a trace of the desired product (149) (EQUATION 37).



EQUATION 37.

2.4.3.3 REVERSIBILITY.

A very recent report by Fráter and co-workers[151] on an intramolecular variant of the Baylis-Hillman reaction assessed the utility of chiral phosphine catalysts in addition to the common nitrogen bases (EQUATION 38).



2 1

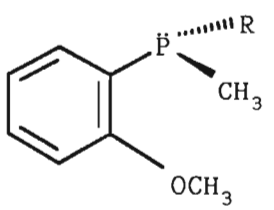
EQUATION 38.

Attempts to transform 2 to 1 under the most common conditions, resulted in only formation of *cis*-1. Their results are listed in TABLE 8.

TABLE 8: Cyclisation experiments of 2 to 1.

Entry Catalyst, Solvent[a]	Time	Mol%cat.	%2	%1	Remarks
1 DABCO	32d	15	81	-	19% cis-2
DABCO, THF	30d	37	80	-	20% cis-2
2 $NaOC_2H_5$, C_2H_5OH, (-30° → rt)	2h	100	10	-	40% 4[7]
3 LiTMP[b], ether (-50° → rt)	1d	3	10	-	a.o. 5[7]
4 Quinidine, C_2H_5OH, THF	10d	10	100	-	
5 Li-quinidinate, HMPA	5h	25	0	0	mixture of unidentified products
6 $(n\text{-}Bu)_3P$	1d	25	25	75(GLC)	isolated 39% 1
7 $(CH_3)_2(C_6H_5)P$	1d	25	35	65(GLC)	
8 " CH_3CN	5d	30	70	30(GLC)	
9 $(i\text{-}Bu,CH_3,C_6H_5)P$	30d	25	50	50	
10 $CH_3(C_6H_5)_2P$	40d	25	100	-	
11 (-)PAMP(6, 78%ee)[8]	20d	20	100	-	
12 (-)CAMP(7, 62%ee)[8]	10d	18	25	75(GLC)	isolated 40% 1 (14%ee)[c]

a) if not otherwise mentioned, reactions were carried out without solvent at room temperature; b) Lithium-2,2,6,6-tetramethylpiperidide; c) NMR, optishift, CH_3-triplet of the ester group separated, $[\alpha]_D^{20}$ 0°(c=1,EtOH).

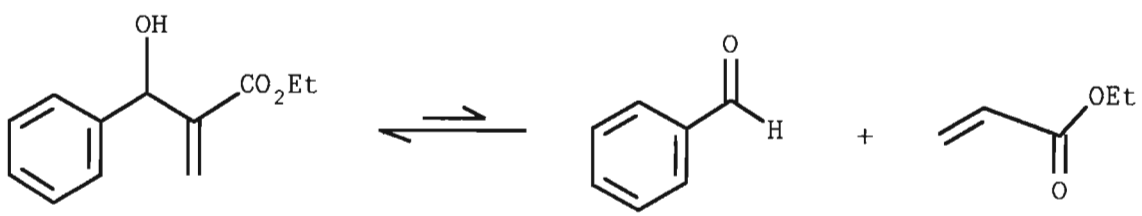


6 R = C_6H_5; (-)-PAMP

7 R = $c\text{-}C_6H_{11}$; (-)-CAMP

Although the use of chiral phosphine catalysts was found to be more useful than the corresponding nitrogen bases, the e.e.'s obtained were low.

An interesting observation was that when 2 is treated with 0.25 equivalents of dimethylphenylphosphine, an *equilibrium mixture* consisting of 65% of 2 and 35% of 1 is formed. In addition, it was noted that treatment of (150) with DABCO, during six days, also afforded an equilibrium mixture of (150) (87%) and benzaldehyde (EQUATION 39).



(150)

EQUATION 39.

Thus, the low e.e.'s obtained were attributed[151] to the possible reversibility of the C-C bond formation (EQUATION 38).

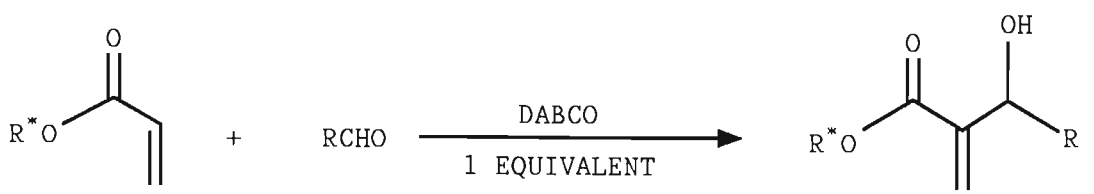
Their results also indicate the following:

(1) Higher conversion of 2 to 1 during shorter reaction times.
(2) Although only two reactions were carried out with chiral catalysts (ENTRIES 11 and 12), *induction* was at least observed for the faster reaction (ENTRY 12).

Thus, on the basis of the above findings, we can predict comparatively much lower diastereoselectivities for our

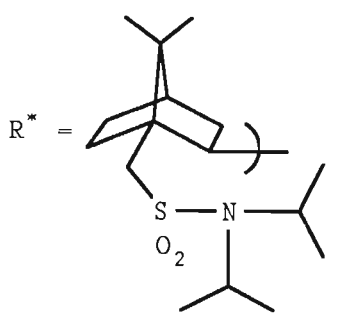
coupling reactions that were "slow". Inspection of our results (TABLE 5) indicates that the latter is true for ENTRIES 1, 14-17, 19, 22 and 23. By analogy, the reactive α-chiral adehydes (and/or together with superior catalysts with respect to reaction rate), should lead to higher degrees of diastereoselectivity through shorter (faster) reaction times. Our results indicate that this is relevant for ENTRIES 1 vs 2-8 (TABLE 5). However, superior diastereoselectivity observed in ENTRY 9 cannot be rationalised although the observed reaction time of 1.3 months is indicative of a slow reaction. It is also evident that the faster reactions (ENTRIES 10-13) result in lower diastereoslectivities.

Recently, Basavaiah *et al.*[89] reported the DABCO-induced diastereoselective coupling (7-20% d.e.) of chiral acrylates with achiral aldehydes to produce the corresponding 2-(1-hydroxyalkyl)acrylates (SCHEME 26).

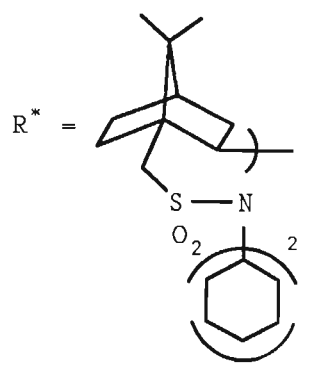


(83)

(151)



(152)



(81)

SCHEME 26.

Their results are tabulated in TABLE 9.

TABLE 9: Preparation 2-(1-hydroxyalkyl)acrylates from chiral acrylates and aldehydes.

ENTRY	ACRYLATE	ALDEHYDE RCHO	PRODUCT	YIELD (%)	TIME (DAYS)	d.e. (%)
1	151	MeCHO	83	83	7	11
2	151	EtCHO	83	78	7	16
3	151	$(Me)_2CHCHO$	83	77	14	7
4	151	FURFURAL	83	85	0.75	20
5	151	PhCHO	83	89	7	15
6	152	MeCHO	83	70	2	30
7	152	EtCHO	83	70	7	42
8	152	PhCHO	83	84	10	15
9	81	EtCHO	83	85	10	70
10	81	PhCHO	83	80	15	25

It is observable that, in general, the slower reactions resulted in lower diastereoselectivities (e.g., ENTRIES 1 vs 6).

Similar work by Isaacs and co-workers[85], however, under conditions of *high pressure*, led to products with up to 100% d.e., as indicated in TABLE 10.

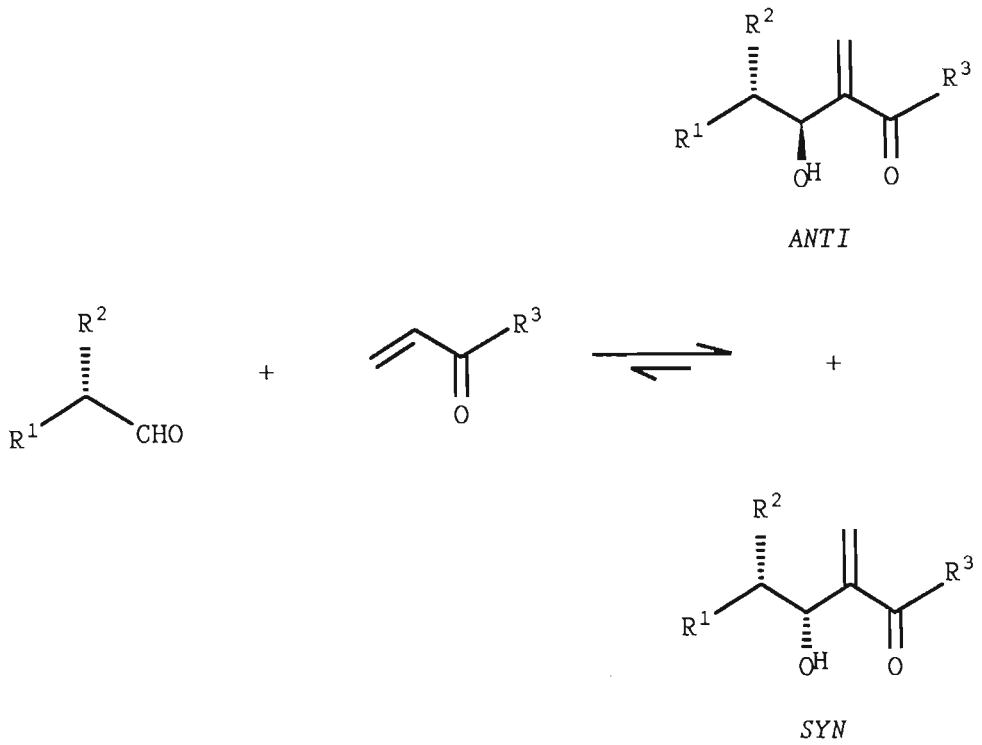
TABLE 10: Diastereomeric excess in reactions betwen chiral acrylates and aldehydes, catalysed by DABCO.

acrylic ester	aldehyde	r*	p/kbar	T/°C	t/h	Yield/%	de/%
(-)-menthyl	acetaldehyde	1:11	7	30	113	36	16
(-)-menthyl	acetaldehyde	1:1	0.001	16	430	95	14
(-)-bornyl	acetaldehyde	1:5	5.5	26	21	48	-
(-)-nopyl	acetaldehyde	1:4	5.5	26	21	30	36
(-)-menthyl	thiophene-2-aldehyde	1:4	6	27	144	52	-
(-)-menthyl	furfural	1:4	0.001	17	1150	15	17
(-)-menthyl	naphth-aldehyde	1:4	6	27	140	57	23
(-)-menthyl	benzaldehyde	1:4	0.001	17	1150	93	22
(-)-menthyl	benzaldehyde	1:4	7.5	30	21	42	100
(-)-menthyl	p-tolualdehyde	1:4	0.001	17	1150	30	100
(-)-menthyl	p-tolualdehyde	1:4	8.5	31	46	31	87
(-)-menthyl	p-ethylbenz-aldehyde	1:4	8.5	31	46	32	94
8-phenyl menthyl	benzaldehyde	1:4	8	35	70	31	86

* (r = molar ratio of acrylate to aldehyde)

These results (TABLE 10) indicate that higher diastereoselectivities were observed for the faster reactions. Furthermore, a comparison of these results with that obtained by Basavaiah *et al.*[89] (TABLE 9) indicates that for the acetaldehyde/benzaldehyde-menthyl acrylate coupling, superior d.e.'s were achieved by Isaacs and co-workers[85] (TABLE 10) due to shorter reaction times.

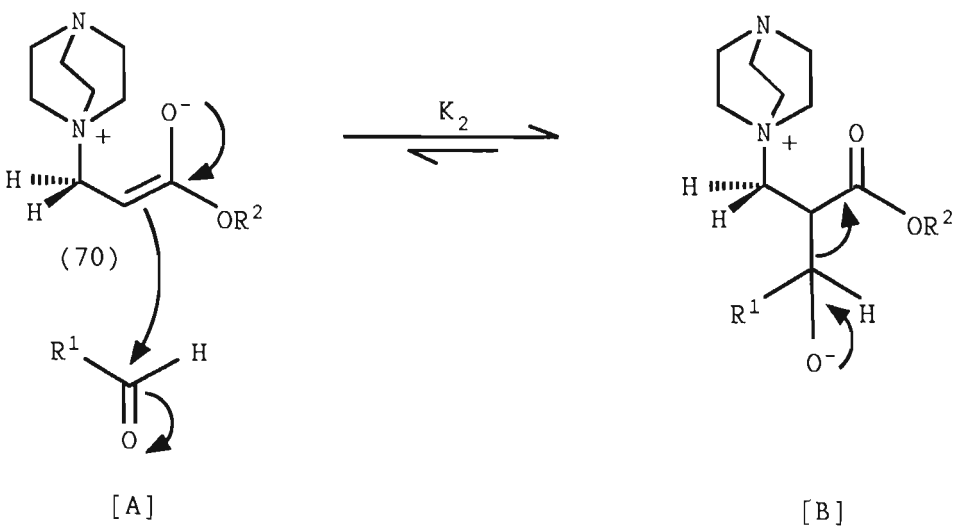
An obvious conclusion one can draw with respect to asymmetric induction in the Baylis-Hillman reaction is that achievement of superior results is not favoured due to its reversibility (EQUATION 18).



EQUATION 18.

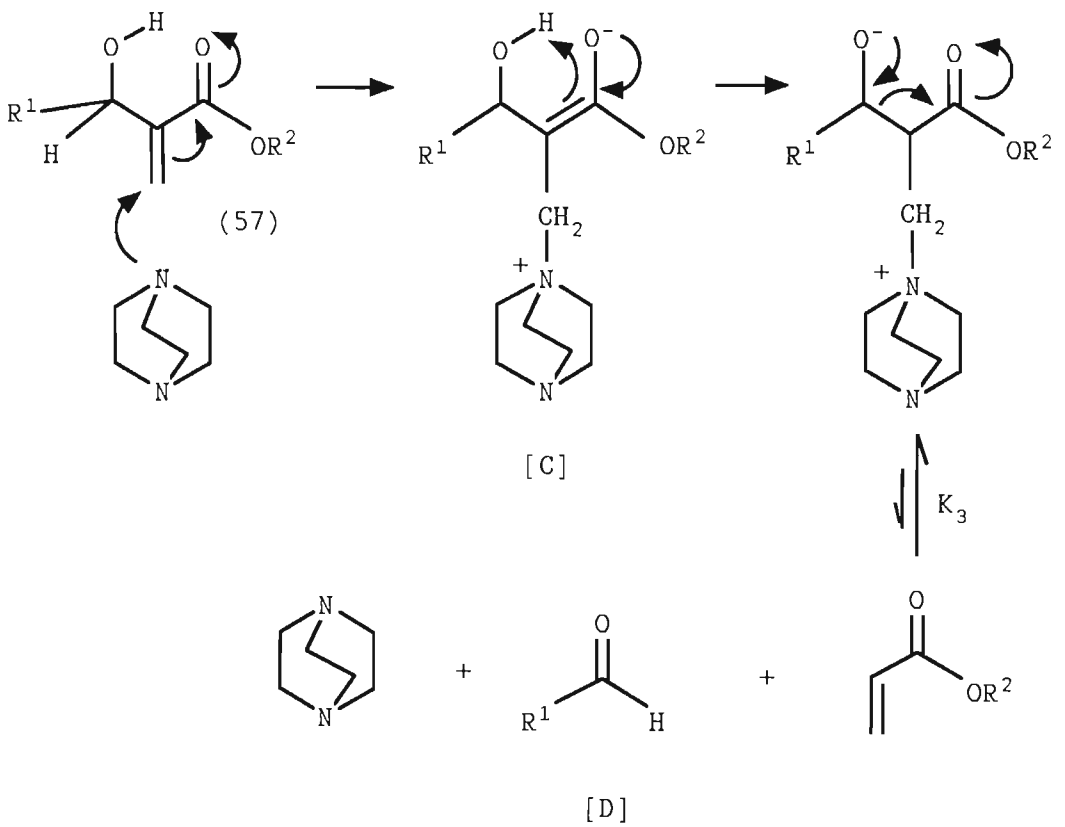
In view of the proposed mechanism,[82,139] reversibility is possible at 2 stages:

(1) At the initial coupling stage, where the dipolar enolate species attacks the electrophilic carbonyl carbon (SCHEME 27).



SCHEME 27.

(2) Subsequent reversibility after formation of the coupled hydroxy acrylate (product) as observed by Fráter and co-workers[151] (SCHEME 28).



SCHEME 28.

We propose the following "overall" reaction "equilibrium" profile (SCHEME 29).

SCHEME 29.

For enantioselective reactions, it is more difficult to predict the relative stabilities of [A], [B], [C] and [D]. Results by Fráter and co-workers[151] indicate that the initially formed product [C] appears to be more stable. For diastereoselective reactions, the predominance of either the *anti* or *syn* isomer [C] under these reversible conditions, is also influenced by other factors affecting the diastereoselectivity (e.g., steric effects - nature of R^1, $R^2$and R^3), which might affect [A] and [B], in addition to the relative stabilities of the *anti* and *syn* diastereomers.

These observations that, in general, the faster catalysed coupling reactions lead to higher asymmetric induction, lends added support to the previous mechanistic proposals[82] with respect to the rate-determining step in the Baylis-Hillman reaction, viz., attack of the dipolar enolate species onto the electrophilic carbonyl carbon of the aldehyde.

Thus, factors which promote kinetic control of the latter reaction, particularly those which lead to an enhancement of k_2, should, ideally, lead to highly enantioselective reactions, and thus reducing the degree of reversibility. However, due to the catalytic nature of this reaction, (elimination of the catalyst after formation of the hydroxy acrylate), reversibility at this stage cannot be entirely eliminated.

2.4.3.4 ASSIGNMENT OF STEREOSUBSTRUCTURE.

The structural assignment to *cis/trans* isomers of variously substituted cyclic compounds is traditionally effected by n.m.r. spectroscopy. However, the asssignment of *syn/anti* diastereomers of acyclic compounds is more difficult.[20] This

problem of being able to assign the correct stereostructure to *syn/anti* components of diastereomer mixtures has been addressed by a number of groups[152-154] in recent years and various diagnostic n.m.r. shift correlations have thus emerged. The latter is particularly relevant for those classes of compounds in which intramolecular hydrogen bonds favour one particular cyclic conformation, for example, β-hydroxycarbonyl compounds.[34,152]

Existing methods in the literature will be reviewed in the discussion that follows, with emphasis on some of their shortcomings, in general, and also as applied to our systems.

2.4.3.4.1 EXISTING METHODS AND THEIR SHORTCOMINGS.

2.4.3.4.1.1 VICINAL COUPLING CONSTANTS BY H^1 N.M.R. (METHOD A).

Valence bond theory has been of great success in qualitatively describing trends in $^3J_{H,H}$. The situation is clearly rather complex because of the considerable number of electrons and geometrical parameters involved. The most important feature is that when other factors are constant, the *vicinal* coupling constant through carbon is predicted to depend on the dihedral angle (Φ) between the C-H bonds, as shown in EQUATION 40, where A, B and C are constants with approximate values 4.0, -0.5 and 4.5, respectively.

$$^3J = A + B\cos(\Phi) + 2\cos(2\Phi)$$

EQUATION 40.

However, use of these values usually underestimates ^3J, and a better empirical set for hydrocarbons is found to be A = 7, B = -1 and C = 5 Hz.[155] This variation of ^3J with Φ is shown in FIGURE 33.

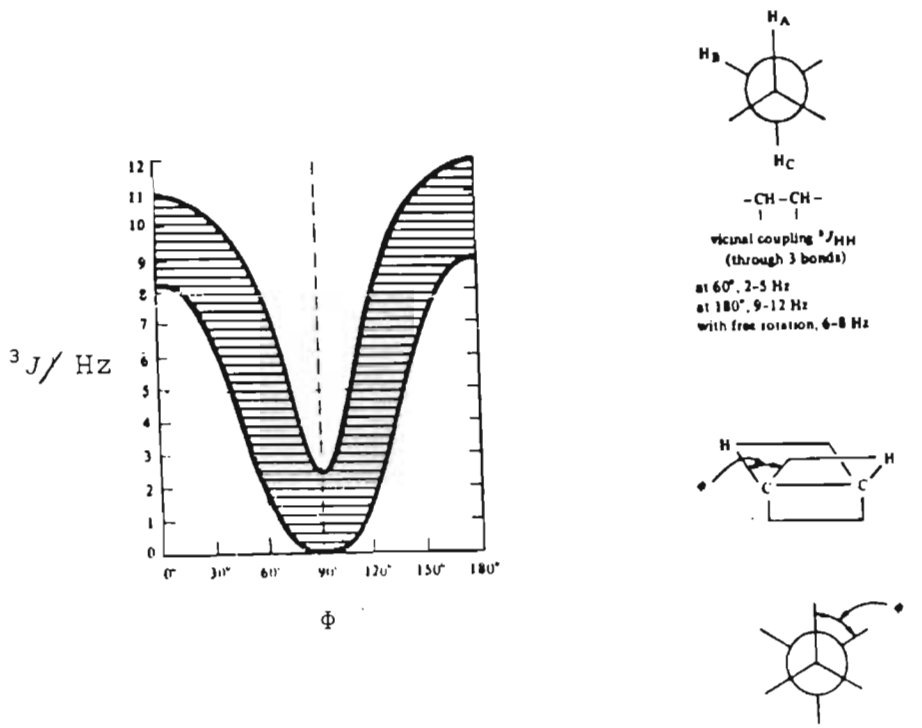


FIGURE 33.

EQUATION 40 is known as the Karplus equation[156] and has been used to predict the dihedral angles in compounds of unkown conformation. However, there are considerable dangers in this procedure since the Karplus model is only valid in the absence of electronegative substituents and of departure from tetrahedral angles at carbon. Thus, qualitative use of EQUATION 40 is useful, particularly when values of A, B and C are determined from model compounds closely related to the unknown, whereas quantitative use is to be avoided.

Experimentation[155] shows that vicinal (H,H) coupling constants increase in the order:
gauche (Φ = Π/3) < cis (Φ = 0) < trans (Φ = Π), in the absence of other influences than Φ.

Valence bond calculations also make the following predictions[155] which agree with experimental observation - though the effects are not independent:

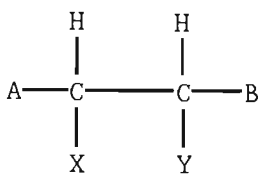
(1) Electronegative substituents decrease ^{3}J.

(2) Increase of HCC bond angles decreases ^{3}J.

(3) Increase of C-C bond length decreases ^{3}J.

Karplus-type equations are not general for nuclei other than hydrogen but they have been developed for several classes of coupling, e.g., ^{13}C and ^{1}H, and have reasonable validity provided closely similar compounds are treated, multiply-bonded atoms are excluded, and the coupled nuclei do not possess lone pairs.

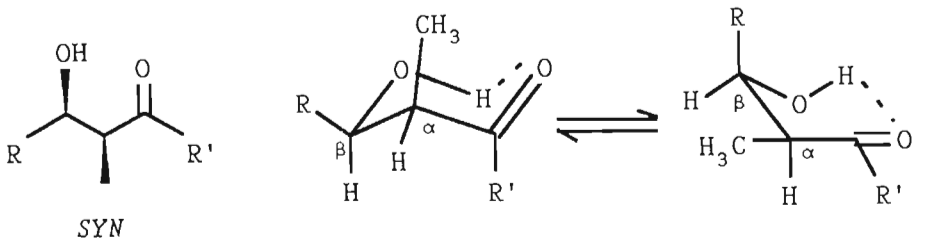
Several studies[34,157] have shown that the well known relationship between the dihedral angle of adjacent C-H bonds and the spin-spin coupling contants of the protons can be used to obtain information about the preferred conformations of a pair of diastereomers of the type *(X)*.



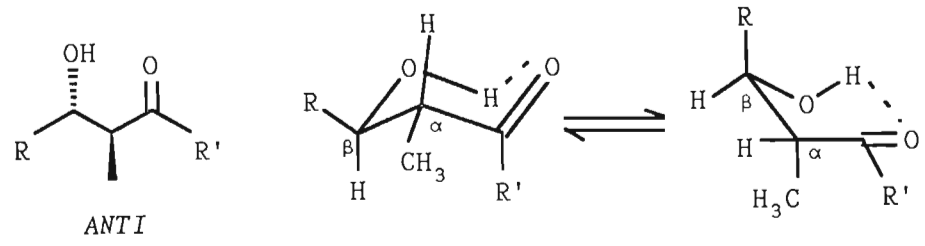
(X)

VICINAL COUPLING CONSTANTS OF β-HYDROXYCARBONYL COMPOUNDS.

If there is a hydrogen at both the α and the β-carbon atoms relative to the carbonyl group, and if both stereoisomeric aldols exist in an intramolecularly hydrogen-bonded conformation, then the vicinal coupling constant J_{AB} is less for the *syn* isomer (2-6 Hz), than for the *anti* isomer (7-10 Hz)[34,157] (SCHEME 30).



(153) (153a) (153b)



(154) (154a) (154b)

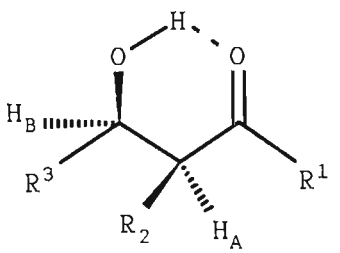
SCHEME 30

It has been demonstrated that β-hydroxycarbonyl compounds (153) and (154) exist in an intramolecularly hydrogen bonded form.[34,157] Two possible chair-like conformers for such structures are illustrated by structures [(153a) and (153b)] and [(154a) and (154b)] (SCHEME 30).

The observed vicinal coupling constants were rationalised[152] in terms of these structures. The conformational equilibrium for (154) generally favours (154a), in which these protons are held in an *anti* relationship. Consequently, the observed vicinal coupling constant is large (J_{vic} = 7-12 Hz). Conversely, in either of conformer of (153a) or (153b), these protons are held in a gauche relationship, resulting in a small coupling constant (J_{vic} = 0-4 Hz).

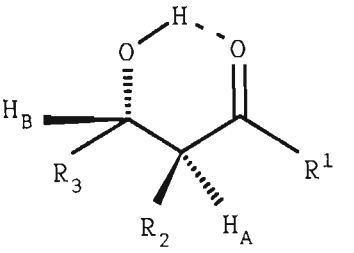
However, as shown by data[53] in TABLE 11, one must exercise caution when using vicinal coupling constants for the

assignment of aldol stereosubstructure because the actual conformer population depends strongly on the nature of R_1, R_2 and R_3 (FIGURE 34).



SYN

(155a)



ANTI

(155b)

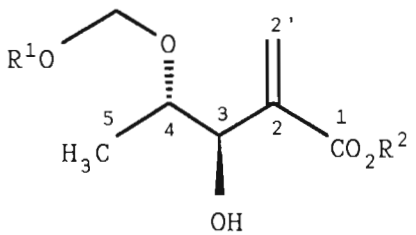
FIGURE 34.

TABLE 11: ^{1}H n.m.r. vicinal coupling constants J_{AB} for β-hydroxycarbonyl compounds (155).

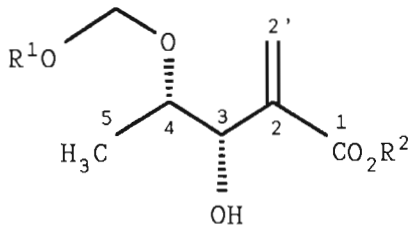
R^1	R^2	R^3	J_{AB} (Hz)	
			SYN	*ANTI*
MeO	Me	Ph	4.7	8.6
MeO	Et	Ph	6.2	8.4
MeO	^{i}Pr	Ph	8.2	6.0
MeO	^{t}Bu	Ph	10.1	4.5

As the size of either R_2 or R_3 increases, the R_2-R_3 gauche interaction becomes more important.

VICINAL COUPLING CONSTANTS OF α-METHYLENE-β-HYDROXY-γ-ALKOXY ESTERS

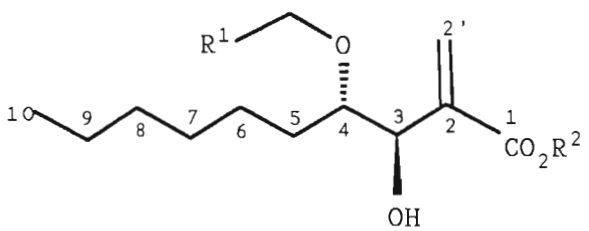


ANTI



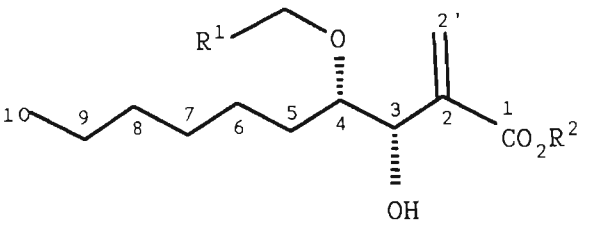
SYN

2: R^1 = $PhCH_2$; R^2 = Me
3: R^1 = $PhCH_2$; R^2 = Me
4: R^1 = $PhCH_2$; R^2 = ^{t}Bu
5: R^1 = $PhCH_2$; R^2 = ^{t}Bu
6: R^1 = CH_3; R^2 = Me
7: R^1 = CH_3; R^2 = Me
8: R^1 = $CH_3O(CH_2)_2$; R^2 = Me
9: R^1 = $CH_3O(CH_2)_2$; R^2 = Me



ANTI

10: R^1 = $PhCH_2$; R^2 = ^{t}Bu
12: R^1 = CH_3; R^2 = Me
14: R^1 = CH_3; R^2 = ^{t}Bu



SYN

11: $R^1 = PhCH_2$; $R^2 = {}^tBu$

13: $R^1 = CH_3$; $R^2 = Me$

15: $R^1 = CH_3$; $R^2 = {}^tBu$

FIGURE 35.

TABLE 12: Vicinal coupling constants between H-3 and H-4 for compounds **2-15.**

COMPOUND	CONFIGURATION	*J* (H-3,H-4)(Hz)
2	*ANTI*	4.0
3	*SYN*	4.7
4	*ANTI*	4.2
5	*SYN*	4.8
6	*ANTI*	4.0
7	*SYN*	4.2
8	*ANTI*	3.6
9	*SYN*	5.0
10	*ANTI*	7.5
11	*SYN*	4.2
12	*ANTI*	7.0
13	*SYN*	7.0
14	*ANTI*	7.0
15	*SYN*	7.0

TABLE 12 shows data obtained by Banfi *et al.*[153] for the title compounds **2-15** (FIGURE 35).

The observation that $^{vic}J_{syn} > {}^{vic}J_{anti}$ has been noted in some amino alcohols, glycols and hydroxy ethers.[158]

It is evident that $(J_{syn} > J_{anti})_{H-3/H-4}$. It is also evident that the vicinal coupling constants between H-3 and H-4 cannot be used for stereochemical assignment as their values are too close. However, it was noted that these values are in agreement with preferred conformations proposed.

However, utilisation of the above method has its shortcomings, viz. :

(1) The coupling constants of both diastereomers are required for assignment of stereosubstructure.
(2) Initial determination of the coupling constant from the ^{1}H n.m.r. spectrum requires relatively purified (that is, the method is not particularly applicable to the direct investigation of crude reaction products), and in most cases, separated diastereomers and/or diastereomer mixtures. Subsequent purification may result in isolation of only one of the possible two diastereomers. Furthermore, the desired separation of diastereomers is not always possible.
(3) Depending on additional coupling constants from R_2 and R_3, and/or the hydroxyl proton (FIGURE 34), the relevant coupling constants are not always easily obtained.

In a number of our systems, the above problems were experienced in addition to the following:

(4) Failure to achieve adequate resolution of the required resonances (masking, overlapping, etc., of other resonances).

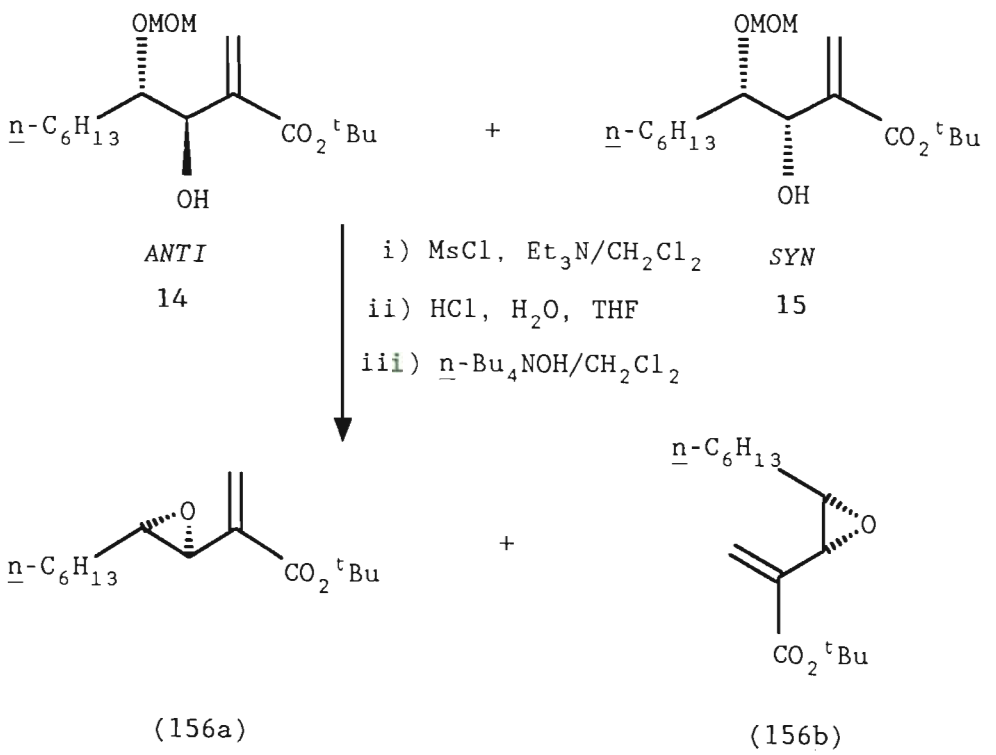
(5) In some cases, the coupling constants were virtually of the same order of magnitude and/or did not follow the expected trends, e.g., $J_{anti} > J_{syn}$.

Clearly, for a range of compounds such as these, such a protocol is not generally attractive or efficient.

CONVERSION INTO A CYCLIC DERIVATIVE FOLLOWED BY N.M.R. STUDIES.

Proton vicinal coupling constants have been previously used for *cis/trans* assignment of epoxides.[59]

The configuration of the α-methylene-β-hydroxy-γ-alkoxy esters **2-15** (FIGURE 35) was further proved by transformation into the epoxides (156a) and (156b), by Banfi *et al.*[153] (SCHEME 31).



SCHEME 31.

The vicinal coupling constant between H-3 and H-4 showed that (156a) (J = 2.1 Hz) is *trans* while (156b) (J = 4.6 Hz) is *cis*, so that **14** is *anti* and **15** is *syn*.

The above method requires, initially, a fair amount of substrate (diastereomer mixture/separated diastereomers) for the subsequent chemical transformations, which as in our systems, the corresponding yields of products (hydroxy acrylates/enones) ranged from good to poor, and can thus be a problem. Another drawback is the tedious chromatographic separations that need to be carried out after each step. Such a protocol is obviously not worth pursuing for a range of diasteremeric pairs.

We initially attempted the above reaction sequence (SCHEME 31) on the diastereomeric mixture (131) with, however, very little success.

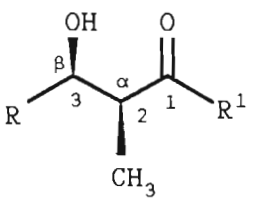
2.4.3.4.1.2 ^{13}C N.M.R. SHIFTS OF α-METHYL, β-HYDROXYCARBONYL COMPOUNDS (METHOD B).

For pairs of isomers in which both compounds exist in hydrogen bonded conformations, ^{13}C n.m.r. spectroscopy may be employed for the assignment of relative configuration. This technique is particularly useful for aldols in which R_2 is methyl (FIGURE 34) because the methyl resonance is easy to find in the ^{13}C n.m.r. spectrum.

Heathcock *et al.*[152] have recorded the ^{13}C n.m.r. spectra for over 40 sets of β-hydroxycarbonyl compounds possessing diastereoisomerism. Empirical observations allowed the assignment of stereosubstructure to these compounds.

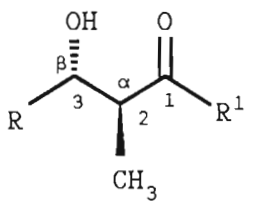
THE α-METHYL-β-HYDROXYCARBONYL COMPOUNDS.

With the α-methyl, β-hydroxycarbonyl compounds (153) and (154) (FIGURE 36/SCHEME 30), Heathcock *et al.*[152] obtained the following results (TABLE 13).



SYN

(153)



ANTI

(154)

R = Ph, *p*-NO_2Ph, *p*-MeOPh, Et, ^{i}Pr, ^{t}Bu, $(Ph)_2CH$, $PhCH(CH_3)$.

R^1 = H, OH, *O*-alkyl, ^{i}Pr, ^{t}Bu, Et, Ph, $C(CH_3)_2OMe_3Si$, mesityl.

FIGURE 36.

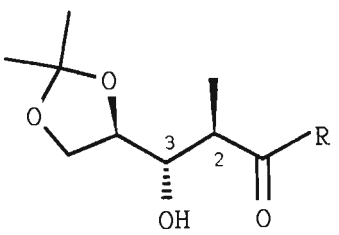
TABLE 13: Chemical shift ranges for diastereomeric β-hydroxycarbonyl compounds (153) and (154).

CARBON	CARBINOL (C-3)	METHINE (C-2)	METHYL
SYN	71.6-78.1	38.6-53.8	7.6-12.9
ANTI	74.0-82.5	40.8-55.2	10.9-17.9

An upfield shift of the carbons were observed for the *syn* isomer compared with those in the *anti* isomer. A slight overlap was also noted in the carbinol and methyl signals between the ranges for a given isomer in all the compounds studied.

The upfield shifts of the methyl groups in *syn* diastereomers (153) were rationalised[152] by comparing the number of gauche interactions in the conformers [(153a) and (153b)] and [(154a) and (154b)] (SCHEME 30). The source of this shielding is the additional gauche interaction between the methyl group and the C-O bond in (153a) and between R and the C_{α}-C-O bond in (153b). ^{1}H n.m.r. evidence of (154a) indicated that this conformer is highly unfavoured. Nevertheless, an evaluation of its gauche effects still allowed them to predict that methyl groups in the *anti* isomers will resonate downfield.

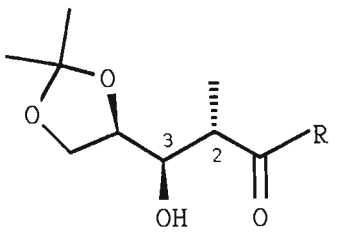
Heathcock *et al.*[149] also assigned stereosubstructures to a mixture of four β-hydoxy esters [(157a)-(157d)] (FIGURE 37) which were subsequently separated by chromatography into *anti* [(157a) and (157b)] and *syn* [(157c) and (157d)] fractions, on the basis of ^{13}C n.m.r. chemical shifts of the C-2 methyl groups, which are shown under the appropriate structures.



14.6 ppm

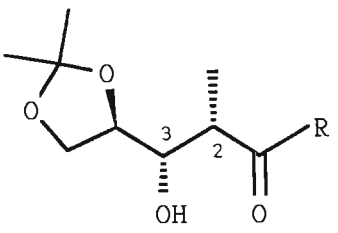
(157a)

ANTI (C_2, C_3)



12.5 ppm

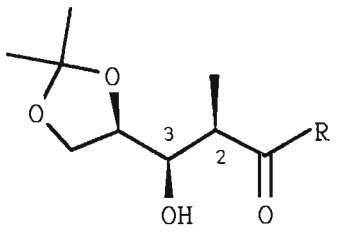
(157b)



9.1 ppm

(157c)

SYN (C_2, C_3)



9.1 ppm

(157d)

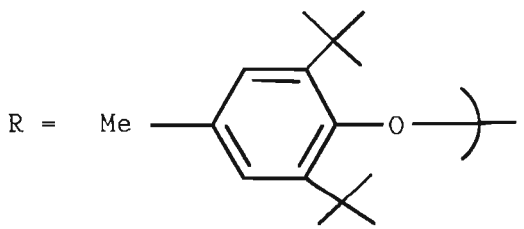


FIGURE 37.

It was previously shown[152] that this resonance is of diagnostic value for assigning *syn/anti* stereostructure to aldols.

Each fraction was then reduced to a mixture of diols which showed characteristic ^{13}C n.m.r. chemical shifs for the C-2 methyl group, shown under appropriate structures (FIGURE 38).

13.5 ppm *ANTI* (C_2, C_3) 14.2 ppm

10.2 ppm *SYN* (C_2, C_3) 10.4 ppm

FIGURE 38.

Stereostructures to aldols in FIGURE 39 were also assigned by ^{13}C n.m.r., by Heathcock *et al.*[149] where it was noted that the C-2 methyl resonances occurred at 10.1 (*syn*) and 14.0 (*anti*) ppm.

SYN (C_2, C_3) *ANTI* (C_2, C_3)

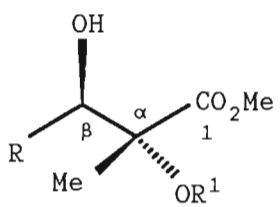
FIGURE 39.

It follows that, like the vicinal coupling constant criterion, this ^{13}C n.m.r. chemical shift correlation method should break down if steric repulsions are sufficiently large so that one diastereomer does not exist predominantly in an intramolecularly hydrogen-bonded conformation.

However, comparisons suggest that the ^{13}C n.m.r. criterion may be more reliable for assigning relative configuration than the vicinal coupling constant method.

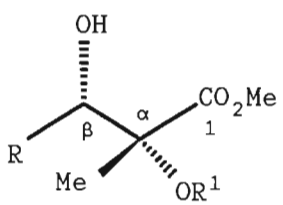
THE α-ALKOXY, α-METHYL-β-HYDROXYCARBONYL COMPOUNDS.

The signals of interest for determining the stereostructure of α-alkoxy aldol adducts (158a) and (158b) (FIGURE 40) are the carbinol, methyl and the carbonyl carbons.



SYN

(158a)



ANTI

(158b)

R = Et, ^{i}Pr, ^{t}Bu, Ph, PhCH(Me)

R^1 = H, Bz, Me, MEM

FIGURE 40.

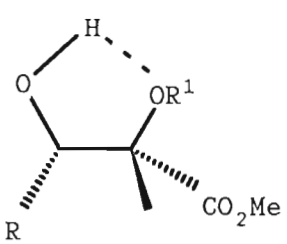
The data, obtained by Heathcock *et al.*,[152] are summarised in TABLE 14.

TABLE 14: Chemical shift ranges for β-hydroxycarbonyl compounds (158a) and (158b).

CARBON	CARBINOL (C-β)	METHYL	CARBONYL (C_1)
SYN	77.1-82.5	16.1-23.3	172.6-176.3
ANTI	77.0-82.1	14.9-24.6	172.5-177.9

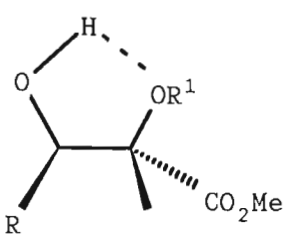
These data indicate that the *anti* carbonyl and the *syn* carbinol resonances *generally* appear downfield of the corresponding resonances in their diastereomers. In all the compounds investigated, the methyl resonance of the *syn* diastereomer was downfield of the comparable resonance for the *anti* diastereomer.

This upfield shift in the ^{13}C n.m.r. spectrum of the *anti* isomer (158b) was explained[152] by the shielding effect of the *cis*-alkyl group in (158b) (FIGURE 41), that is, *via* a five-membered hydrogen-bonded ring structure.



SYN

(158a)



ANTI

(158b)

FIGURE 41.

Application of ^{13}C n.m.r. shifts to these hypothetical structures would indicate that, for the methyl groups, the more sterically congested isomer (158b) would resonate upfield, as is indeed observed.

Furthermore, in the carbonyl resonances, the more sterically congested isomer (158a) would be expected to appear upfield, again, as is observed.

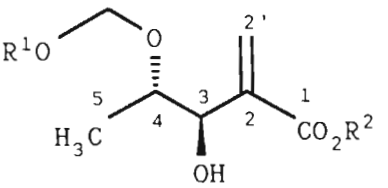
Their data also showed that coincidence of resonances occurs for (158a) and (158b) much more often than for aldols (153) and (154) (FIGURE 36). It is also evident from the data in TABLE 14 that the chemical shift ranges for corresponding carbons in the *syn* and *anti* diastereomers are virtually identical. Clearly, both isomers must be available for examination before reliable assignments may be made for the α-alkoxy aldol adducts.

The above method also has its fair share of drawbacks. An obvious one is again the requirement of purified diastereomer mixtures and/or separated diastereomers for the analysis. Besides the fact that the mixtures could not be separated in some instances, the observed chemical shifts did not always follow the expected trends.

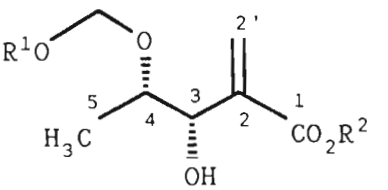
2.4.3.4.1.3 N.M.R. SHIFTS OF α-METHYLENE-β-HYDROXY-γ-ALKOXY ESTERS (METHOD C).

Banfi *et al.*[153] found very characteristic, steric-related shifts in the ^{13}C and ^{1}H n.m.r. spectra which provided an efficient tool for the configurational assignment for the above-mentioned class of compounds.

The most characteristic ^{13}C shifts of pentanoates **2-9** (FIGURE 35), are listed in TABLE 15, and those for compounds **10-15** (FIGURE 35), are shown in TABLE 16.



ANTI



SYN

2: R^1 = $PhCH_2$; R^2 = Me
3: R^1 = $PhCH_2$; R^2 = Me
4: R^1 = $PhCH_2$; R^2 = ^{t}Bu
5: R^1 = $PhCH_2$; R^2 = ^{t}Bu
6: R^1 = CH_3; R^2 = Me
7: R^1 = CH_3; R^2 = Me
8: R^1 = $CH_3O(CH_2)_2$; R^2 = Me
9: R^1 = $CH_3O(CH_2)_2$; R^2 = Me

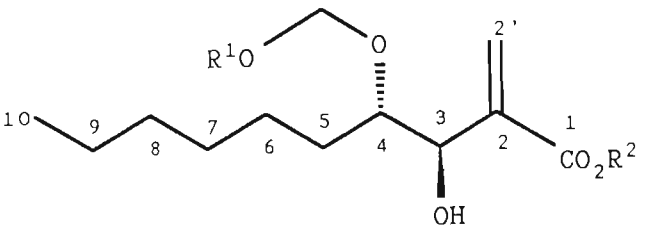
FIGURE 35.

TABLE 15: Selected ^{13}C n.m.r. shifts (δ ppm) of diastereomeric pentanoates **2-9** in $CDCl_3$.

Selected ^{13}C NMR shifts (δ ppm) of diastereomeric α-methylidene-β-hydroxy-γ-alkoxypentanoates in $CDCl_3$[a]

Carbon	2 anti	3 syn	4 anti	5 syn	6 anti	7 syn	8 anti	9 syn
2	139.3	140.6 (+1.3)	140.5	142.0 (+1.5)	139.0	140.6 (+1.6)	139.2	140.6 (+1.4)
2'	126.7	126.4 (−0.3)	125.7	125.5 (−0.2)	126.7	126.5 (−0.2)	126.5	126.5 (0)
3	72.8	73.8 (+1.0)	73.1	74.3 (+1.2)	72.9	74.2 (+1.3)	72.3	74.1 (+1.8)
4	74.6	75.9 (+1.3)	74.9	76.6 (+1.7)	74.7	76.5 (+1.8)	75.5	76.5 (+1.0)
5	13.8	17.1 (+3.3)	14.1	17.3 (+3.2)	13.9	17.3 (+3.4)	13.8	17.2 (+3.4)
OCH_2O	93.0	93.6 (+0.6)	93.1	93.8 (+0.7)	95.2	95.9 (+0.7)	94.3	94.7 (+0.4)

[a] $\Delta(\delta_{syn} - \delta_{anti})$ in parentheses.

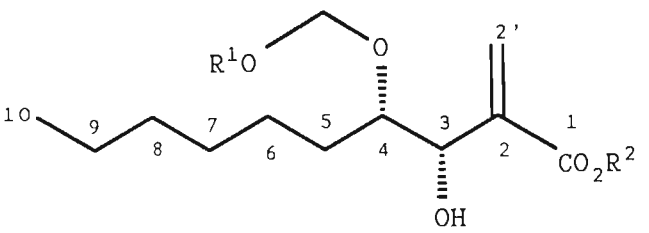


anti

10: $R^1 = PhCH_2$; $R^2 = {}^tBu$

12: $R^1 = CH_3$; $R^2 = Me$

14: $R^1 = CH_3$; $R^2 = {}^tBu$



syn

11: $R^1 = PhCH_2$; $R^2 = {}^tBu$

13: $R^1 = CH_3$; $R^2 = Me$

15: $R^1 = CH_3$; $R^2 = {}^tBu$

FIGURE 35.

TABLE 16: Selected ^{13}C n.m.r. shifts (δ ppm) of diastereomeric decanoates **10**-**15** in $CDCl_3$.

Selected ^{13}C NMR shifts (δ ppm) of diastereomeric α-methylidene-β-hydroxy-γ-alkoxydecanoates in $CDCl_3$.[a]						
Carbon	**10** *anti*	**11** *syn*	**12** *anti*	**13** *syn*	**14** *anti*	**15** *syn*
2	140.5	142.4 (+1.9)	139.1	141.0 (+1.9)	140.7	142.6 (+1.9)
2'	125.6	125.1 (−0.5)	126.7	126.1 (−0.6)	125.6	125.1 (−0.5)
3	72.2	72.3 (+0.1)	72.1	72.1 (0)	72.2	72.2 (0)
4	80.0	81.0 (+1.0)	80.2	80.9 (+0.7)	79.9	81.2 (+1.3)
5	28.9	31.7 (+2.8)	28.9	31.8 (+2.9)	28.9	31.8 (+2.9)
OCH_2O	94.1	94.8 (+0.7)	96.4	96.9 (+0.5)	96.2	96.9 (+0.7)

[a] Δ ($\delta_{syn} - \delta_{anti}$) in parentheses.

It was observed that in **2-15**, the signals of C-2, C-3, C-4 and C-5 of the *anti* isomers are always shifted *upfield* compared with the same carbons of the *syn* isomer. The most sensitive differences are those of C-5 (Δ 2.8-3.4 ppm) and C-2 (Δ 1.3-1.9 ppm). This behaviour was explained by assuming that the preferred conformation is that which permits an intramolecular hydrogen bond between the hydroxy group and the alkoxy group (FIGURE 42).

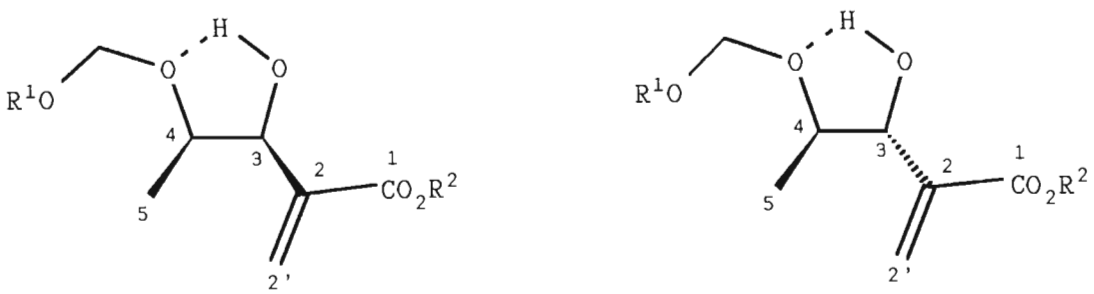


FIGURE 42.

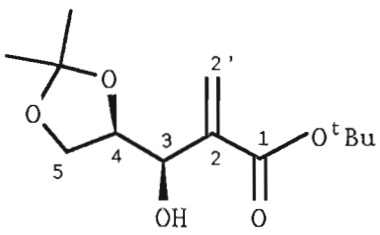
This assumption is in agreement with previous data.[153] The *anti* isomer is thus more sterically congested and, consequently, the C-2 and C-5 carbon signals are shifted upfield. The higher steric compression is also responsible for the upfield shift of C-3 and C-4. In contrast, the C-2' carbons are always shifted *downfield* in the *anti* isomer. On assuming a preferred conformation in which the hydrogen-bonded acceptor is one of the carbonyl oxygens, i.e., a six-membered ring, it is more difficult to ratonalise their spectroscopic data, especially the large shift differences for C-5 and C-2 and also the vicinal coupling constants between H-3 and H-4 (TABLE 12).

It was also observed[153] that the ^1H chemical shifts of the

C-5 methyl groups in pentanoates **2-9** showed a regular *upfield* shift of *ca.* 0.10 ppm between the *anti* and *syn* isomers, which was again attributed to steric compression of the methyl group in the *anti* compounds.

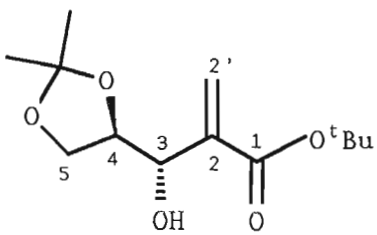
Although it was not claimed by these authors[153b] to be a generalisation, it is observable that proton chemical shifts for H-3 and H-4 showed a regular downfield shift for the *anti* diastereomer as compared to those for the *syn* diastereomer.

In describing the synthetic opportunities offered by the *anti* α-methylene-β-hydroxy-γ-alkoxy esters, Scolastico and co-workers[81] assigned the configuration of the esters (66) (FIGURE 43) by analogy to the known examples and confirmed it by ^{13}C n.m.r. spectroscopy.



SYN

(66 A)



ANTI

(66 B)

FIGURE 43.

They reported the following data:

^{1}H n.m.r. (80 MHz; $CDCl_3$/TMS) δ/ppm:

	ANTI	*SYN*
$C\underline{H}_3CCH_3$	1.36	1.3
	1.46	1.4
^{t}Bu	1.51	1.47
OH	3.06	2.85
H-3, H-4, H-5	3.86-4.62	3.5-4.6

^{13}C n.m.r. (25.41 MHz; $CDCl_3$/TMS) δ/ppm:

anti: 165.35, 139.78, 129.57, 126.07, 81.55, 76.85, 71.29, 65.35, 28.10, 26.62, 25.24

syn: 165.28, 141.02, 125.75, 109.67, 81.43, 78.21, 71.00, 66.30, 28.10, 26.54, 25.35

Selected carbon shifts can be assigned as follows:

CARBON	*ANTI*	*SYN*
1	165.35	165.28
2	139.78	141.02
2'	129.57	125.75

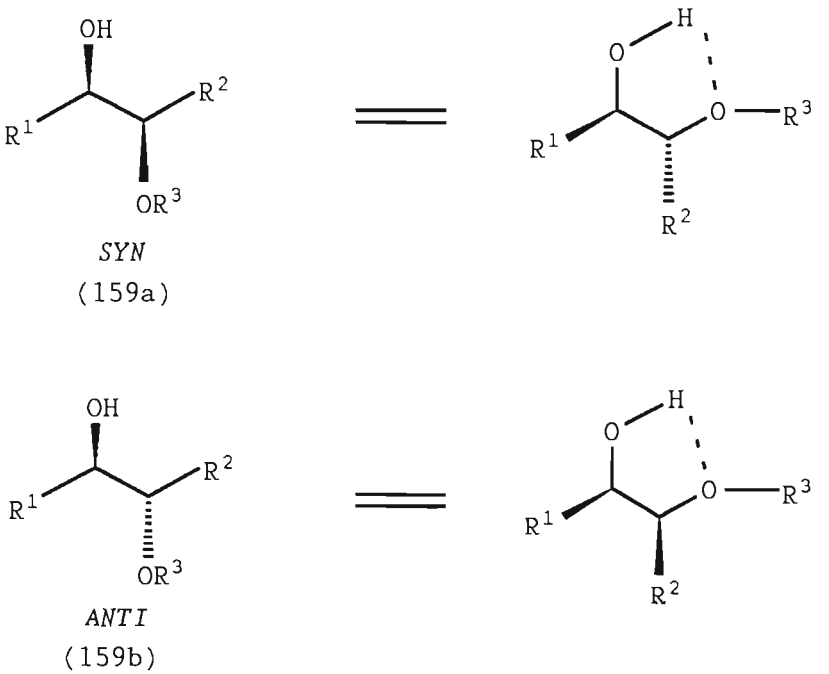
Examination of the ^{1}H n.m.r. data indicate that resonances for the *anti* isomer are shifted downfield in contrast to the upfield shift for the *syn* isomer.

With respect to the ^{13}C n.m.r. data, the *anti* carbonyl occurs downfield to the corresponding *syn* carbonyl, as noted by Heathcock *et al.*[152] Furthermore, C-2' for the *anti* isomer is shifted downfield, as compared to the *syn* isomer, while C-2 for the *syn* isomer is shifted downfield, in accordance with their previous findings.[153]

In addition to the problems experienced with the other methods described above, this protocol also requires relatively purified diastereomer mixtures or separated diastereomers, as well as adequate resolution of specific resonances.

2.4.3.4.1.4 ANALYSIS OF OH SHIFT DIFFERENCES BY ^{1}H N.M.R. (METHOD D).

As outlined above, Heathcock *et al.*[152] surmised the predominance of hydrogen-bonded conformations of the tertiary β-hydroxy ethers which was reflected in the ^{13}C n.m.r. chemical shifts, an effect substantiated by other examples.[154] No significant effect of this nature was, however, found in the ^{13}C n.m.r. spectra of various compounds of the structures (159a) or (159b), representing secondary β-hydroxy ethers (FIGURE 44).



SYN
(159a)

ANTI
(159b)

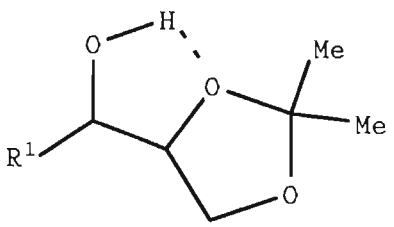
FIGURE 44.

Hoffmann and Landmann[154] examined the chemical shift of the *OH* proton of *syn* and *anti* β-hydroxy ethers which depends on the extent of hydrogen bonding. The extent to which hydrogen-bonded conformations are populated should be larger

for the *syn* (159a) than for the *anti* (159b) isomers[154] (FIGURE 44).

They noted structure-specific differences in the ^1H n.m.r. chemical shifts of the proton, that is, it is diagnostic for the *syn* or *anti* stereosubstructure. The data obtained can be summarised by the statement:
$\delta_{OH}(syn) > \delta_{OH}(anti)$, with the difference amounting to 0.48 ± 0.3 ppm.

This generalisation was also found to hold for a number of compounds of general structure (160).

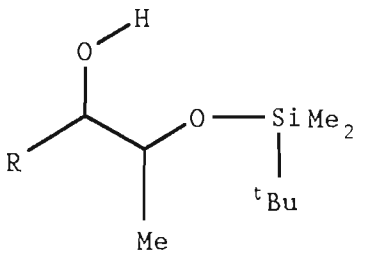


(160)

Another aspect which is affected by the extent and geometry of hydrogen bonding was noted, but turned out not to be general for *all* the compounds examined:
the vicinal coupling constant H-C^1-O-H was found to be larger for the *syn* isomer (≥ 5 Hz) than for the *anti* isomer (≤ 3 Hz).

However, the following limits of the above generalisation are important:

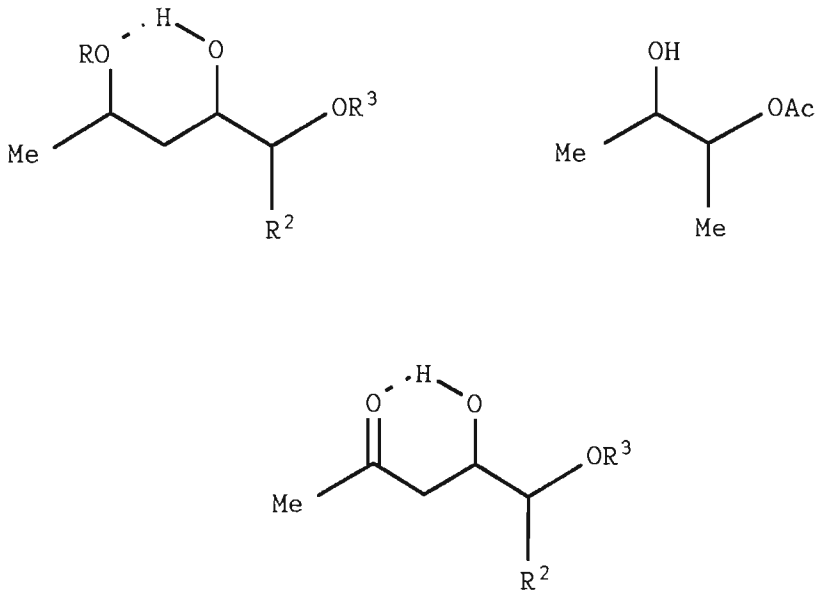
(1) Breakdown of the above-mentioned rule might be confined to cases in which the steric bulk of R^3 is much larger than that of R^2, as indicated below for compound (161).



(161)

R	δ_{OH}/ppm	*SYN*	*ANTI*
CH_3		1.86	2.17
CH_2CHCH_2		2.30	2.30

(2) Since the above generalisation is based on the predominance of hydrogen-bonded structures (159a) and (159b), any structural feature that gives rise to other hydrogen-bonded conformations will render the above rules inapplicable, as in the case of structures depicted in FIGURE 45.



(162)

FIGURE 45.

Application of the above method may require relatively purified diastereomer mixtures. Unfortunately, we noted that these O*H* resonances were not always readily identifiable in all of the systems studied, depending on concentration of the n.m.r. sample, adequate resolution, etc.

For our systems (124), however, the additional structural feature that gives rise to another hydrogen-bonded conformation analogous to (162) (FIGURE 45), in which the hydrogen-bond acceptor is the carbonyl oxygen, is illustrated by (163) (FIGURE 46).

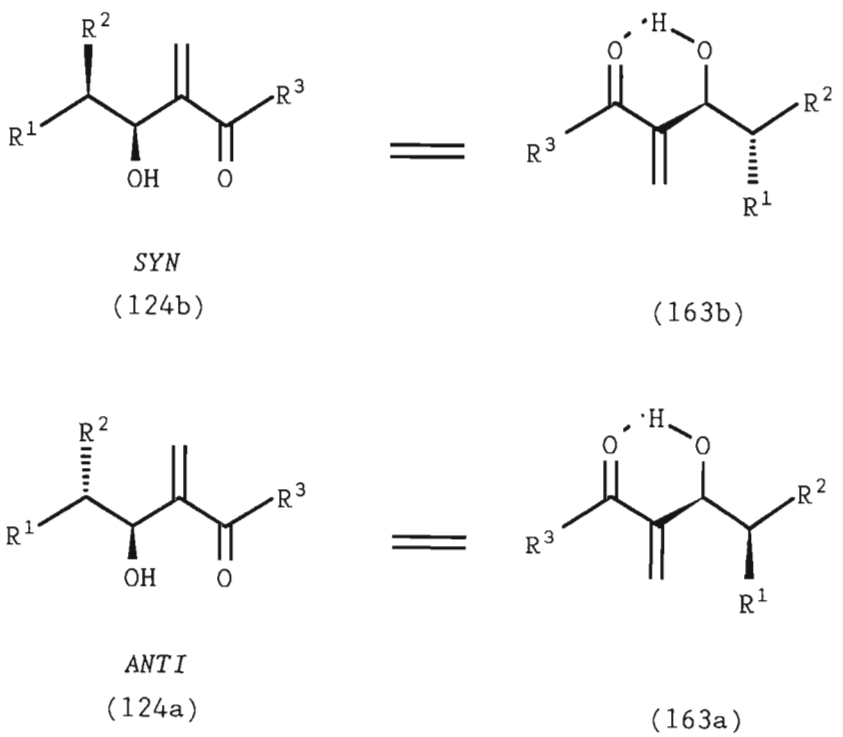


FIGURE 46.

Thus, the above method *cannot* be applied as a tool for stereostructural assignment for our type of compounds.

2.4.3.4.1.5 ANALYSIS OF OH SHIFT DIFFERENCES BY ^{1}H N.M.R. ("PREDICTED" METHOD E).

Following from the above breakdown of the "Hoffmann-Landmann rule"[154] when applied to our systems, we can predict that $\delta_{OH}(anti) > \delta_{OH}(syn)$, on the basis of the alternative hydrogen-bonded conformations (163) (FIGURE 46).

However, as noted earlier, these O*H* resonances were not always readily identifiable and, in some systems, our "predicted rule" above, did not hold, that is, we observed that $\delta_{OH}(syn) > \delta_{OH}(anti)$, in accordance with the Hoffmann-Landmann "rule".

2.4.3.4.1.6 CONVERSION TO PRODUCTS OF KNOWN STEREOSUBSTRUCTURE (METHOD F).

Heathcock *et al.*[149] assigned stereostructures to aldols (164a) (*syn*) and (164b) (*anti*) by conversion to the corresponding lactones (SCHEME 32).

ANTI (C_3, C_4) (164a)

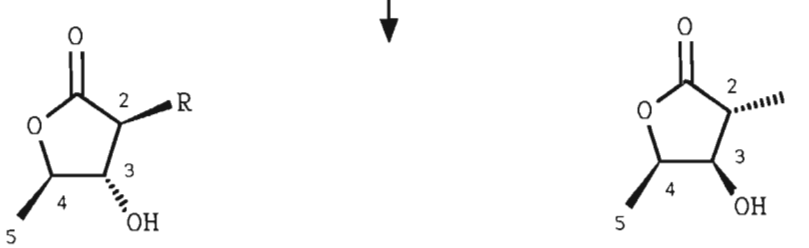
R = Bz, BOM

SYN (C_3, C_4) (164b)

i) MeOH/H_5IO_6

ii) Li/NH_3

iii) H^+



ANTI (C_3, C_4)

R = Me (165a)

R = *n*-C_4H_9 (166)

SYN (C_3, C_4) (165b)

SCHEME 32.

The aldol mixtures were oxidised with periodic acid and the resulting acids subjected to lithium/ammonia reduction to effect hydrogenolysis of the benzyl group. Acidification of the reduction products in each case afforded a separable mixture of lactones (165a) and (165b).

The most diagnostic feature in the spectrum of (165a) is the resonance for the C-3 carbinol proton which appears as a doublet of doublets with J = 7.0 and 8.0 Hz. For lactone (166), the relevant coupling constants are J = 7.0 and 8.5 Hz.

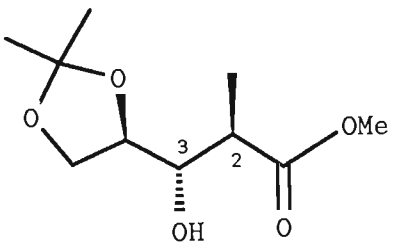
The ^{13}C n.m.r. spectra were also useful in confirming the assigned stereosubstructures. The data are summarised in TABLE 17.

TABLE 17: ^{13}C n.m.r. chemical shifts of the γ-lactones, δ/ppm.

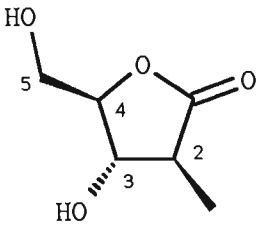
COMPOUND	C-2	C-3	C-4	C-5	C-2 METHYL
165a	43.8	80.1	80.3	17.9	12.4
165b	43.2	75.1	78.3	13.7	12.9
167a	43.2	73.1	84.6	60.0	12.5
167b	39.1	70.1	86.9	60.9	8.3

The relevant diagnostic resonance is the one due to C-5. In the minor lactone (165b), this carbon is shielded by 4.2 ppm by the *cis*-hydroxyl group at C-3.

The stereosubstructures of aldols in SCHEME 33 were rigorously established[149] by conversion into the known lactones (167a) and (167b).



ANTI (C_2, C_3)

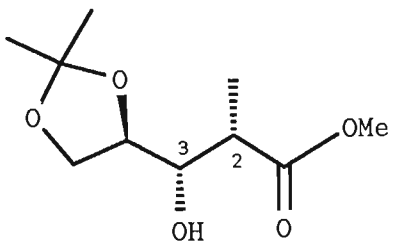


(167a)

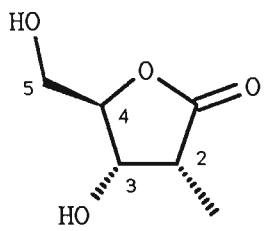
($J_{2H,3H}$ = 8.9 Hz)

ANTI

$HOAc/H_2O$



SYN (C_2, C_3)



(167b)

($J_{2H,3H}$ = 5.9 Hz)

SYN

The ^{13}C n.m.r. chemical shifts of the C-2 methyls of the lactones (167a) and (167b) (TABLE 17) clearly show that the methyl is *cis* to the C-3 hydroxyl in (167b) and *trans* to it in (167a), thus confirming the *syn/anti* nature of the starting aldols.

Application of the above method requires knowledge of compounds with *known* configuration that must be related to

the one in question. This would most surely require a literature search, which is tedious and time-consuming, especially for a range of similar compounds, as in our case. Furthermore, the chemical transformations and subsequent purifications are a potential problem.

2.4.3.4.2 USE OF TAI AS A DIAGNOSTIC TOOL (METHOD G).

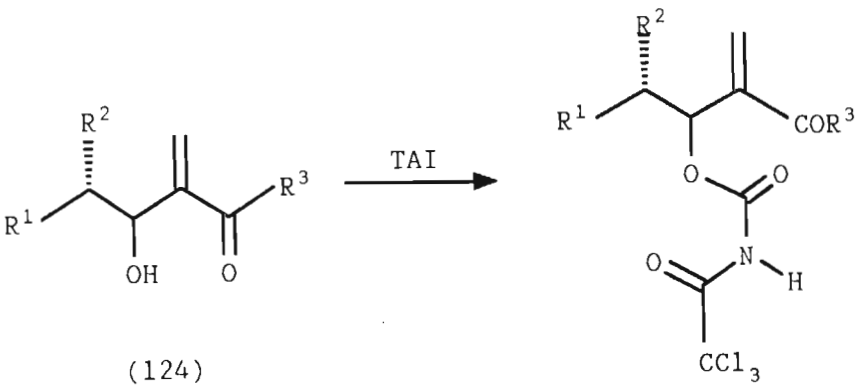
The use of *in situ* formed trichloroacetylisocyanate (TAI) derivatives for the direct measurement of d.e. in our crude reaction mixtures was described[132] earlier (EQUATION 35).

$$\underset{(125)}{CCl_3CONCO} + ROH \rightarrow \underset{(126)}{CCl_3CONHCOOR}$$

EQUATION 35.

This study was then extended to ascertain whether reliable correlations exist between the relative chemical shift values of the carbamate N*H* signals and the *anti/syn* ratios of the substrates. This would then allow for the rapid assignment of the relative stereochemical outcome of these diastereoselective coupling reactions. The present n.m.r.-based methods[152-154,156] depend on the achievement of adequate resolution of specific resonances.

In this and subsequent studies, we have noted a *stereosubstructure*-specific general correlation for the relative chemical shifts of the carbamate N*H* signals that arise from these derivatives (EQUATION 40).

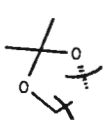


(124) (168)

EQUATION 40.

Data are presented in TABLE 18.

TABLE 18: Carbamate chemical shifts of TAI derivatives (168) of the γ-alkoxy/methyl *anti/syn* diastereomeric mixtures[a] (124).

COMPOUND	R^1	R^2	R^3	δ_{NH} (ppm)[b]		
				SYN[c]	ANTI[c]	$\delta_{SYN} - \delta_{ANTI}$ Δ (ppm)
130	Me	OBz	OMe	8.723	8.590	+0.133
131	Me	OMOM	OMe	8.632	8.503	+0.129
133	Me	OMOM	O^{t}Bu	8.558	8.460	+0.098
134	Me	OBOM	OMe	8.613	8.583	+0.030
64	Me	OBOM	O^{t}Bu	8.613	8.562	+0.051
136	Ph	OMOM	OMe	8.581	8.450	+0.131
137	Ph	OMOM	Me	8.567	8.465	+0.102
138	^{i}Pr	OMOM	OMe	8.690	8.565	+0.125
139	^{i}Pr	OBOM	OMe	8.607	8.486	+0.121
140	^{i}Pr	OBOM	O^{t}Bu	8.618	8.513	+0.105
66			O^{t}Bu	8.829	8.752	+0.077
127	CH_2OBz	OBz	OMe	8.559	8.420	+0.139
142	^{n}Pr	Me	OMe	8.675	8.659	+0.016

[a]Both crude and purified mixtures were analysed.

[b]$CDCl_3$ was used as solvent, (200 MHz; TMS); these shifts are *concentration*-dependent, as stated earlier.

[c]All of these *anti/syn* assignments were corroberated by the traditional spectral methods and/or from the literature, as discussed previously.

This relationship can simply be summarised as:
$\delta_{NH}(syn) > \delta_{NH}(anti)$.

For the above systems (EQUATION 44), the observed differences are in the range +0.03 → +0.14 (TABLE 18). This result is similar to that reported, based on observation of the O*H* signals of secondary β-hydroxy ethers by Hoffmann and Landmann.[154]

FIGURE 47 shows the typical result of such a determination, for the *reported*[68] compound (133).

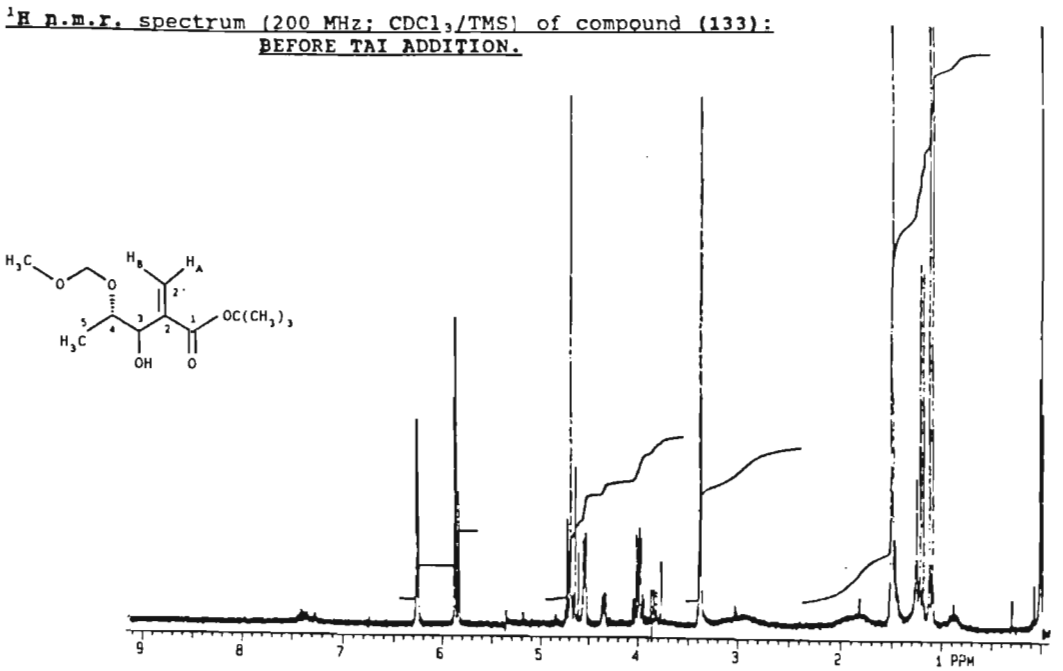


FIGURE 47.

^{1}H n.m.r. spectrum (200 MHz; $CDCl_3$/TMS + *TAI*) of compound **(133): AFTER TAI ADDITION**, showing expanded *carbamate* region (inset).

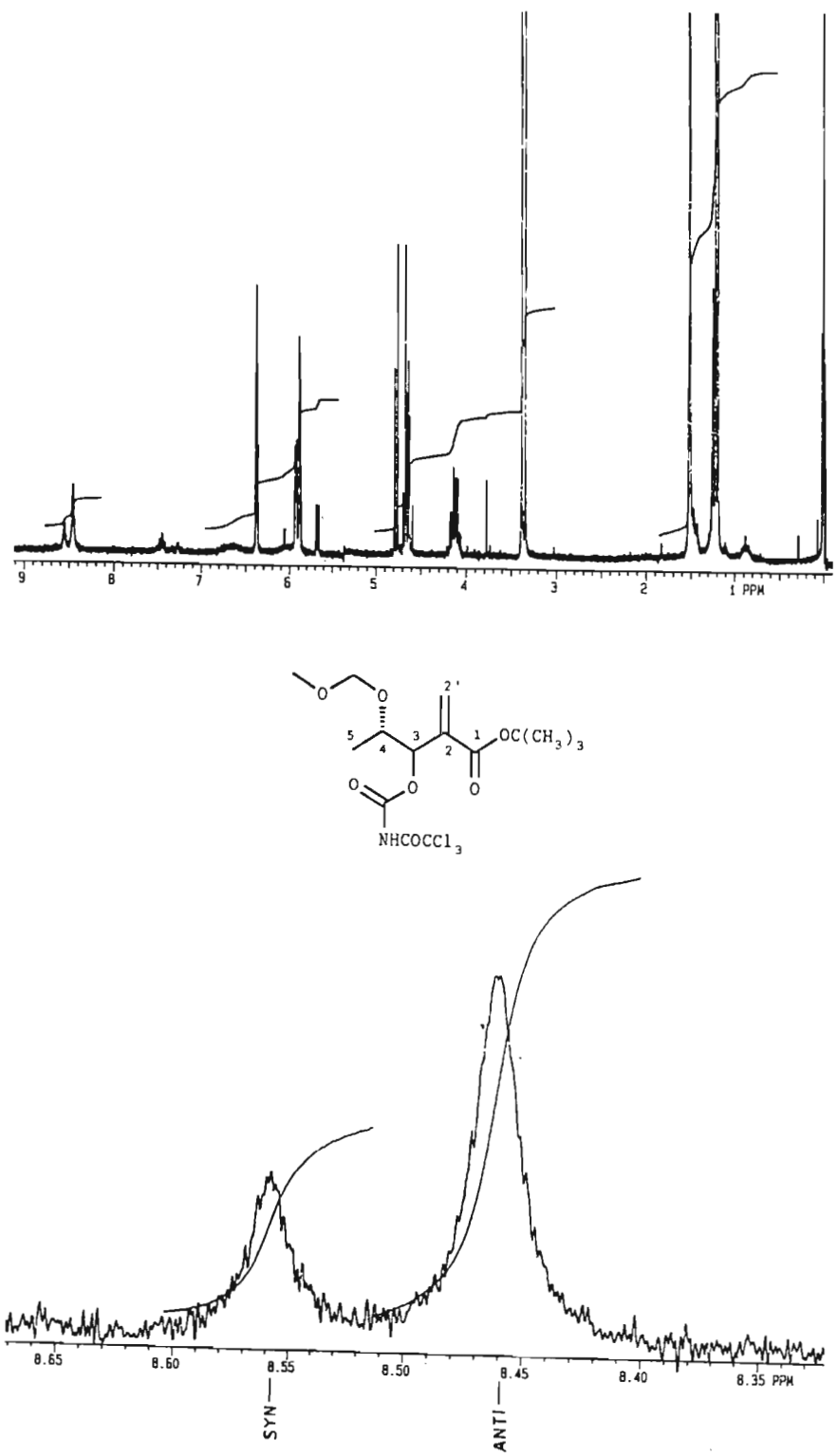


FIGURE 47.

Earlier work[128,130] has suggested a *ZZZ* conformational preference (169) (FIGURE 48) for the TAI derivatives, based on X-ray and dipole studies. This would suggest that, from a study of models, the *syn/anti* shift difference is not attributable to N*H*-heteroatom interactions.

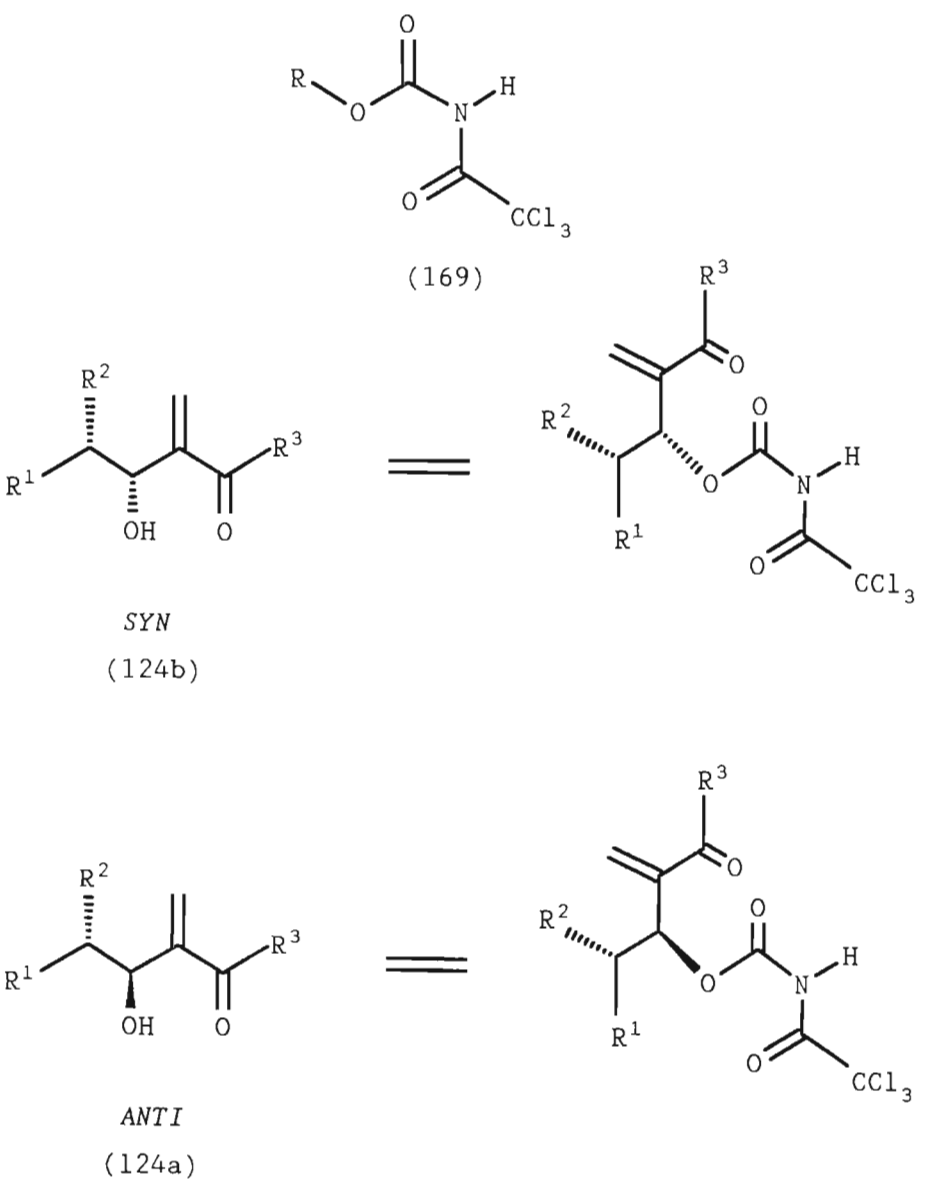
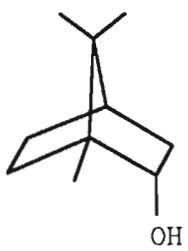


FIGURE 48.

For structure (128),[159] which has no possible sites for significant hydrogen bonding, $\delta_{NH}(syn) > \delta_{NH}(anti)$, as shown below.

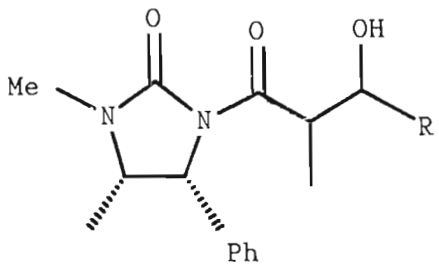


(128)

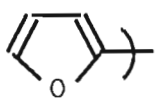
SOLVENT	δ_{NH} (*SYN-ANTI*)/ppm
$CDCl_3$	0
d_6-acetone	+0.088
d_6-benzene	0

Thus, this methodology should obviate the breakdown mentioned above in the case of direct observation of the *OH* resonances.

Compound (129) is a further example of the type of system that has been studied[159] in connection with the observed generalisation for diastereomeric hydroxyl-containing systems. The reported[159] data are shown below.

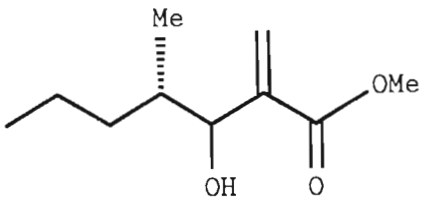


(129)

R	$\delta_{NH}(SYN\text{-}ANTI)$/ppm
Me	+ 0.245
Et	+ 0.232
Ph	+ 0.455
p-NO_2-Ph	+ 0.220
p-OMe-Ph	+ 0.476
	+ 0.487

Although the carbamate N*H* resonance shifts may be solvent and concentration dependent, the relative positions in the uncluttered region of the n.m.r. spectrum, viz., δ 8-10, remain fairly consistent. Compound (128) is the only case reported[159] where solvent induced overlap was observed.

TABLE 19 shows the concentration and solvent dependence of the carbamate shifts for compound (142). These results were obtained as a result of initial problems with achievement of adequate resolution of the carbamate shifts for the compound in question.



(142)

TABLE 19: TAI data for compound (142).

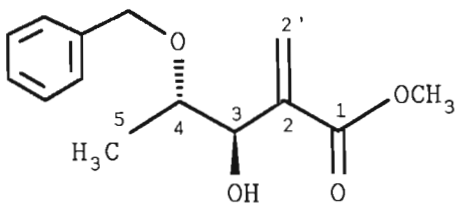
SOLVENT	CONCENTRATION OF (142), (MOL/L)	δ_{NH} (ppm)		
		SYN	*ANTI*	$\Delta(\delta_{SYN}-\delta_{ANTI})$
$CDCl_3$	0.072	8.444	8.444	0
$CDCl_3$	0.162	8.675	8.659	+0.016
$CDCl_3$	0.170	8.617	8.600	+0.017
$CDCl_3$	0.358	8.700	8.700	0
C_6D_6	0.168	8.700	8.700	0

Due to the ease of the experimental method, the simplicity of signal detection and the often attendant secondary spectral simplification, this TAI protocol is a useful additional analytical technique for assignment of *syn/anti* stereosubstructure to diastereomeric mixtures, especially if the study involves a series of related compounds, as is the case with our systems.

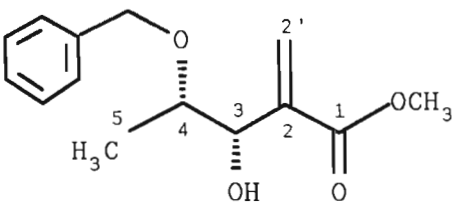
2.4.3.4.3 UTILISATION OF THE DESCRIBED METHODS.

The above methods (A-G) utilised for assignment (relative) of stereosubstructure for the compounds (diastereomer mixtures) listed in TABLE 5, will be indicated under the appropriate structures. Full spectral (n.m.r.) data will be delineated in the *EXPERIMENTAL* section (CHAPTER 5) to avoid repetition.

COMPOUND 130



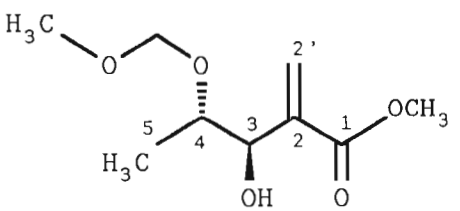
ANTI (MAJOR)
(130 A)



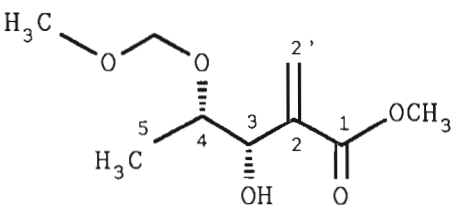
SYN (MINOR)
(130 B)

Methods B, C, E and G.

COMPOUND 131



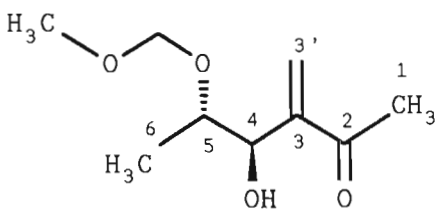
ANTI (MAJOR)
(131 A)



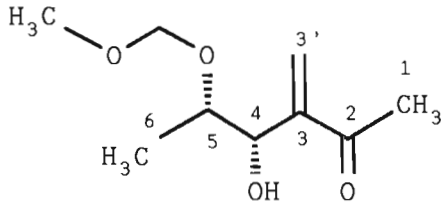
SYN (MINOR)
(131 B)

Methods A, C, D and G.

COMPOUND 132



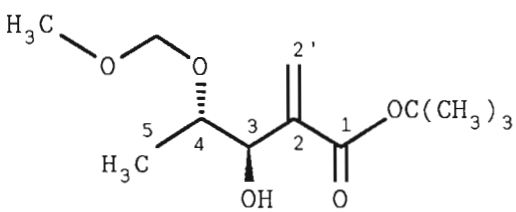
ANTI (MAJOR)
(132 A)



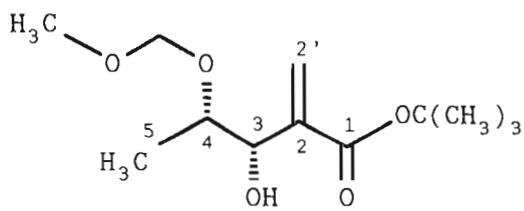
SYN (MINOR)
(132 B)

Method C.

COMPOUND 133



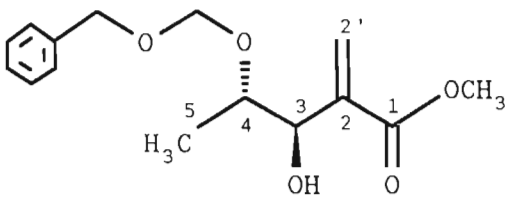
ANTI (MAJOR)
(133 A)



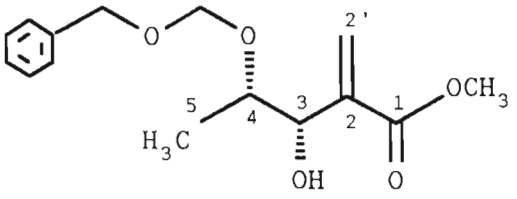
SYN (MINOR)
(133 B)

Methods B, C and G.

COMPOUND 134



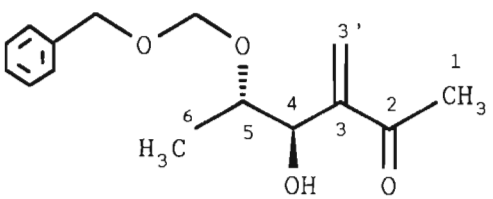
ANTI (MAJOR)
(134 A)



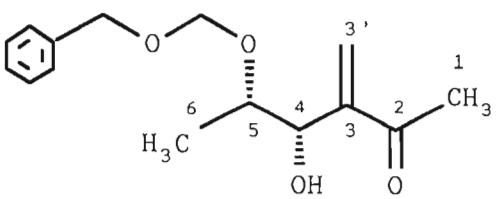
SYN (MINOR)
(134 B)

Methods A, B, C and G.

COMPOUND 135



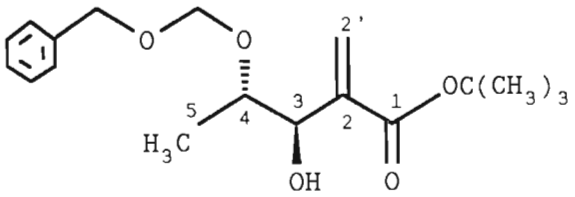
ANTI (MAJOR)
(135 A)



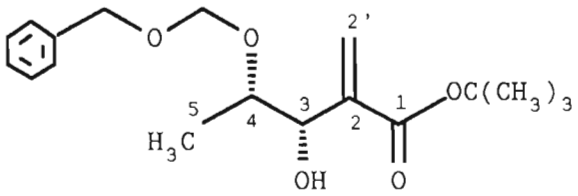
SYN (MINOR)
(135 B)

Methods B and C.

COMPOUND 64



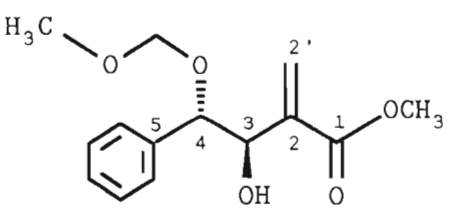
ANTI (MAJOR)
(64 A)



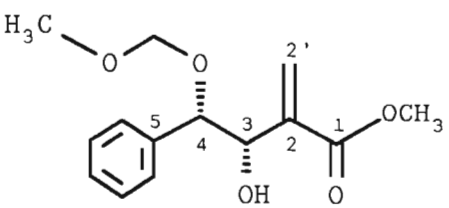
SYN (MINOR)
(64 B)

Methods A, B, C and G.

COMPOUND 136



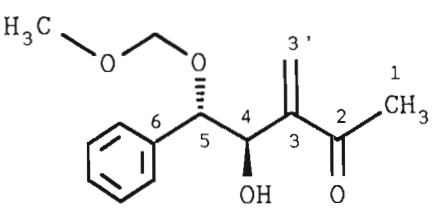
ANTI (MINOR)
(136 A)



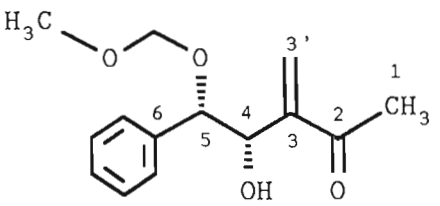
SYN (MAJOR)
(136 B)

Methods A, B, C and G.

COMPOUND 137



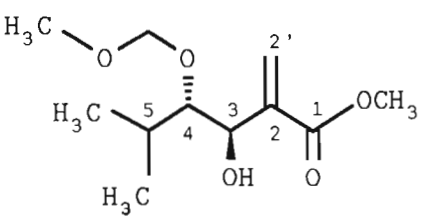
ANTI (MINOR)
(137 A)



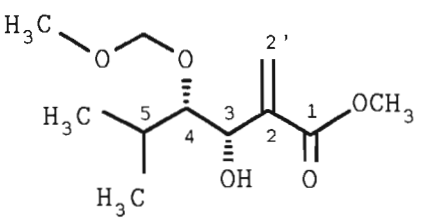
SYN (MAJOR)
(137 B)

Method G.

COMPOUND 138



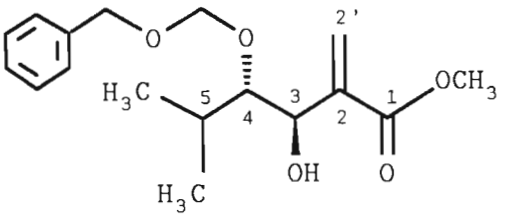
ANTI (MAJOR)
(138 A)



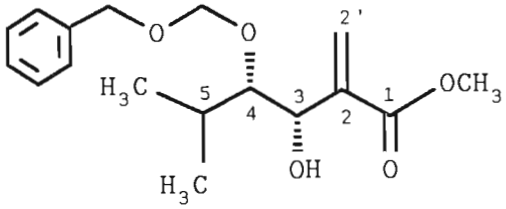
SYN (MINOR)
(138 B)

Methods C and G.

COMPOUND 139



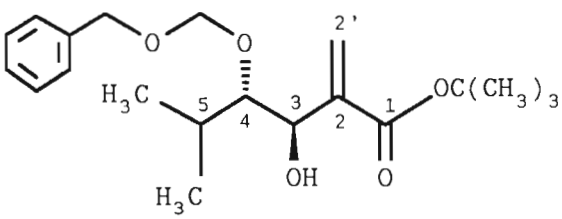
ANTI (MINOR)
(139 A)



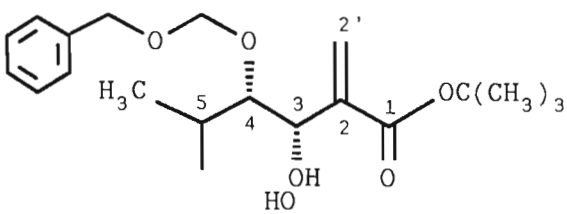
SYN (MAJOR)
(139 B)

Methods B, C, E and G.

COMPOUND 140



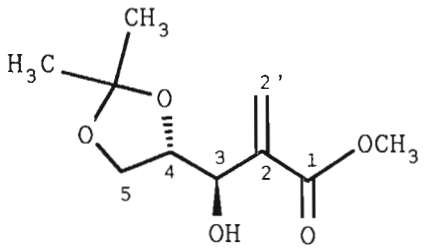
ANTI (MINOR)
(140 A)



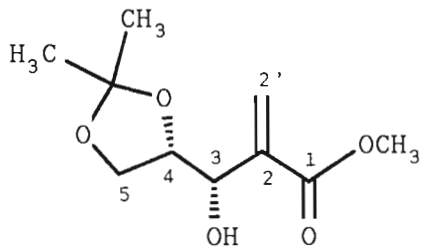
SYN (MAJOR)
(140 B)

Methods C and G.

COMPOUND 141



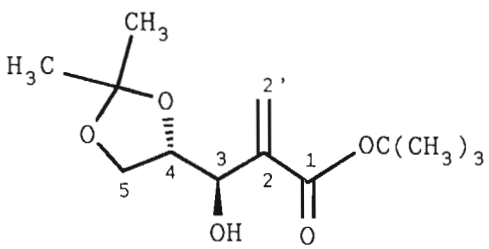
ANTI (MAJOR)
(141 A)



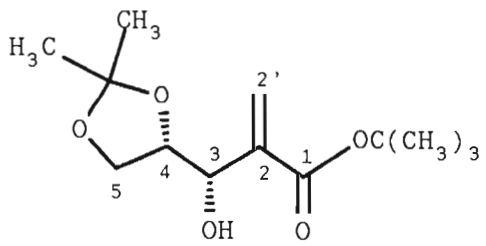
SYN (MINOR)
(141 B)

Methods C and E.

COMPOUND 66



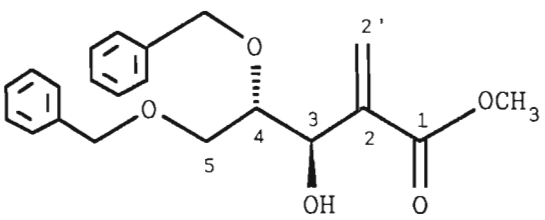
ANTI (MAJOR)
(66 A)



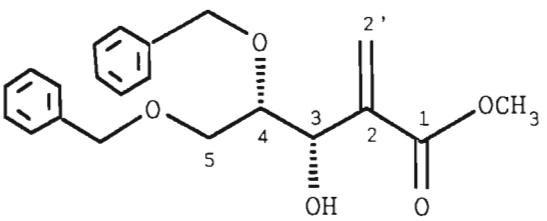
SYN (MINOR)
(66 B)

Methods B, C, E and G.

COMPOUND 127



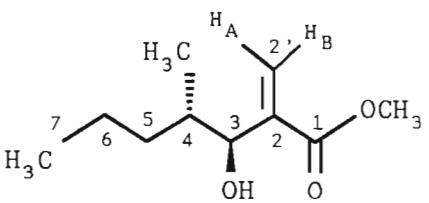
ANTI (MAJOR)
(127 A)



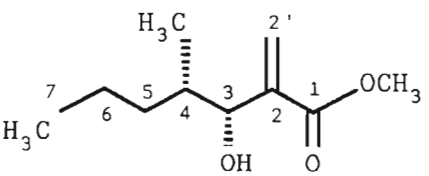
SYN (MINOR)
(127 B)

Methods B, C, E and G.

COMPOUND 142



ANTI (MINOR)
(142 A)



SYN (MAJOR)
(142 B)

Methods B and G.

2.5 ELABORATION OF SELECTED ADDUCTS TO THE α-METHYLENE-γ-BUTYROLACTONES.

2.5.1 POTENTIAL PRECURSORS.

It is evident that the derived α-methylene-β-hydroxy-γ-alkoxy ester systems (124) (FIGURE 49), afforded by the Baylis-Hillman coupling reaction, offers a route to the optically pure α-methylene-β-hydroxy-γ-butyrolactones, as outlined by Scolastico and co-workers[81] (SCHEME 11).

R^1 = Me

R^2 = O-alkyl, O-alkoxyalkyl

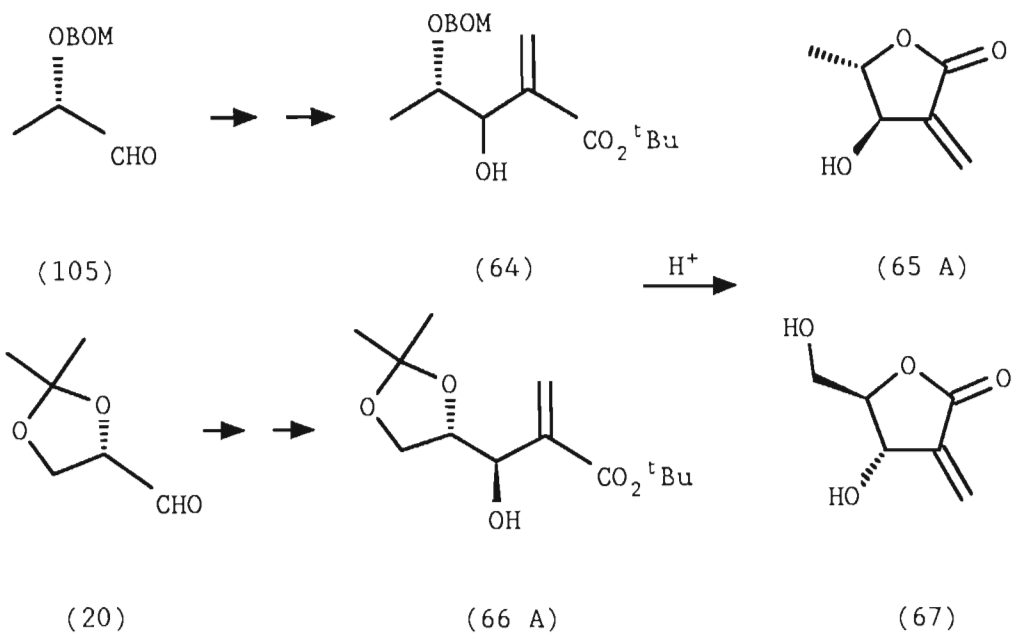
R^3 = OMe, O^{t}Bu

(124)

FIGURE 49.

However, these workers obtained these lactone precursors [(64) and (66 A)] in high d.e., and also in fairly good

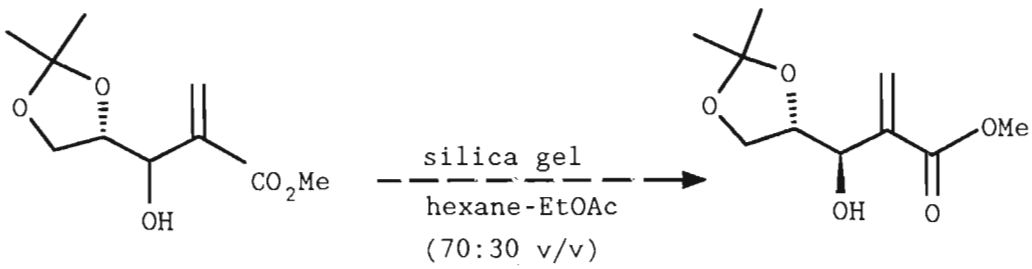
chemical yields from the corresponding α-alkoxy aldehydes (SCHEME 11).



SCHEME 11.

2.5.1.1 ATTEMPTED USE OF THE "GLYCERALDEHYDE" SYSTEM.

Initially, a separation of the major *anti* diastereomer (141 A) from the mixture of methyl-3-hydroxy-2-methylene-4,5-(isopropylidenedioxy)pentanoate (141) was attempted using flash chromatography[105] (SCHEME 34).



~70:30 mixture

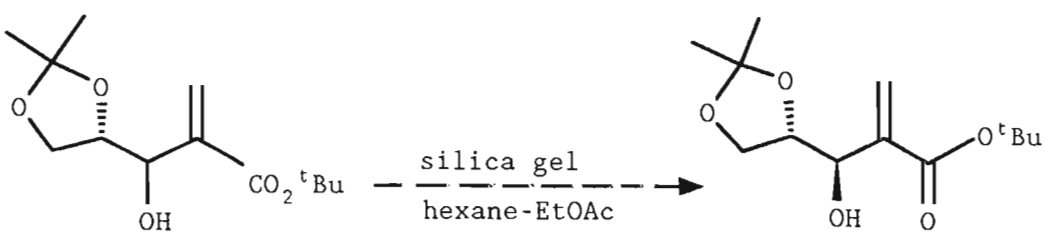
(141)

(141 A)

SCHEME 34.

However, separation was difficult and this was only possible on a scale sufficient for characterisation purposes. Nevertheless, the observed rotation on the major diastereomer (141 A) was $[\alpha]_D^{30}$ = -6.47° (*c* 0.77, $CHCl_3$).

With the corresponding *tert*-butyl pentenoate system (66), the major diastereomer was isolated by chromatography as described by Bernardi *et al.*[81] (SCHEME 35).



(66)

(66 A)

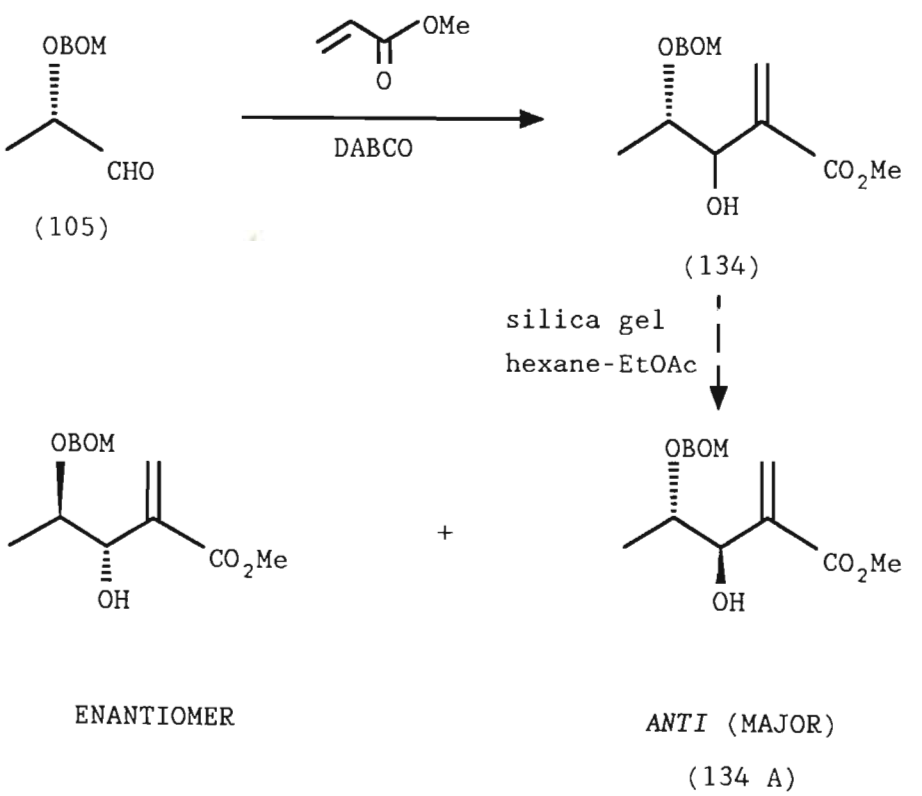
SCHEME 35.

However, the observed optical rotation indicated that the compound was racemic. Cyclisation to the corresponding lactone was therefore not attempted due to the additional

factor that a very small amount of the ester was available for the lactonisation procedure; this would obviously lead to formation of the lactone, but, in *racemic* form.

2.5.1.2 USE OF THE LACTALDEHYDE SYSTEM.

The next system chosen as the precursor to these lactones was the methyl 3-hydroxy-2-methylene-4-(benzyloxymethoxy)-pentanoate system (134), which required preparation of the optically active aldehyde, (S)-2-(benzyloxymethoxy)propanal (105). In this instance, however, it was desirable to utilise the aldehyde in crude form due to its observed tendency to racemise during purification by silica gel chromatography (SCHEME 36).

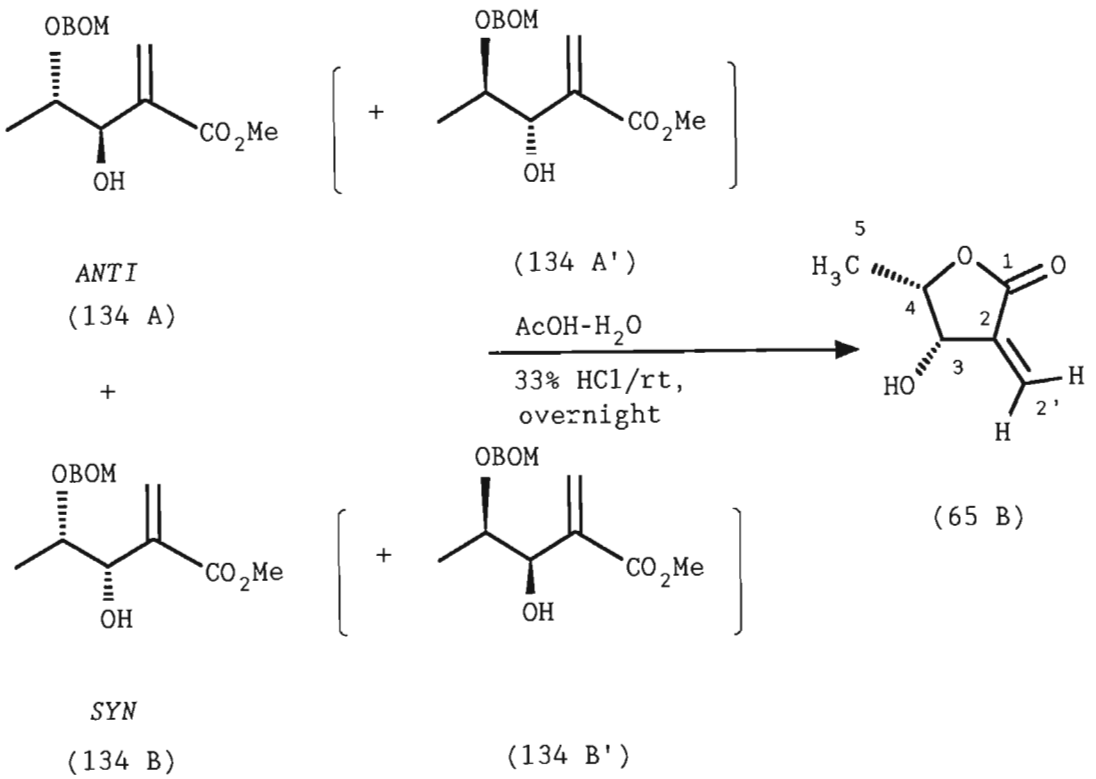


SCHEME 36.

Purification of the methyl pentanoate system (134) led to isolation of the major (*anti*) diastereomer (134 A), again on a scale sufficient for spectroscopic analysis. Its observed optical rotation was $[\alpha]_D^{24}$ = +10.58° (*c* 0.69, $CHCl_3$). However, Scolastico and co-workers[81] reported a value of +15.7° (*c* 1.0, $CHCl_3$). The enantiomeric purity would appear to be about 67%. Since the starting aldehyde (105) was utilised in crude form, without chromatographic separation, and was also noted to be optically active, the only possibility for racemisation of the aldehyde exists during its coupling in the Baylis-Hillman reaction. It is likely that DABCO, under the extended reaction time, is sufficiently basic to promote this racemisation.

2.5.1.2.1 LACTONISATION.

Lactonisation was, nevertheless, attempted on a purified mixture of (134), which obviously contained the two *anti/syn* diastereomers, each existing as an enantiomeric pair (SCHEME 37).

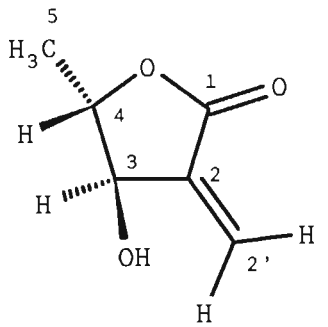


SCHEME 37.

The reported lactonisation procedure was followed, viz., acetic acid-water (4:1 v/v, *conc.*HCl).

2.5.1.2.2. RESULTS AND DISCUSSION.

Purification of the crude product mixture by flash chromatography, led to isolation of only one relatively pure lactone as a *liquid*, together with a small amount of the two lactones (65 A and B). Scolastico and co-workers,[81] however, report spectral data on the major lactone (65 A), which is reported to be a *solid*, with an optical rotation of $[\alpha]_D^{20}$ = -11.07° (*c* 1.02, MeOH). Their[81] reported n.m.r. data are tabulated below (TABLE 20).



(65 A)

TABLE 20: Reported n.m.r. data for lactone (65 A).

^{1}H n.m.r. (80 MHz; $CDCL_3$, D_2O/TMS).

δ(ppm)	NO. OF PROTONS	SIGNAL MULTIPLICITY	COUPLING CONSTANT *J*(Hz)	ASSIGNMENT
1.3	3	d	6.7	$C\underline{H}_3$
4.4	1	q	6.7	$C\underline{H}CH_3$
4.45	1	s	-	$C\underline{H}OD$
5.98	1	d	2	*trans*-$\underline{H}C$=CCO
6.42	1	d	2	*cis*-$\underline{H}C$=CCO

^{13}C n.m.r. (25.14 MHz; $CDCl_3$/TMS), δ/ppm, were listed without assignments:

169.22, 138,83, 125.84, 82.10, 74.17, 19.02.

We obtained the following spectroscopic data on our isolated lactone (65 B) (TABLE 21).

TABLE 21: ^{1}H n.m.r. data (200 MHz; $CDCl_3$/TMS) for our isolated lactone (65 B).

δ(ppm)	NO. OF PROTONS	SIGNAL MULTIPLICITY	COUPLING CONSTANT *J*(Hz)	ASSIGNMENT
1.44	3	d	6.3	$C\underline{H}_3$
3.72	1	broad s	-	CHO<u>H</u>
4.42	1	dq	6.4 & 4.4	$C\underline{H}CH_3$
4.46	1	m	-	C<u>H</u>OH
5.99	1	d	2.0	*trans*-<u>H</u>C=CCO
6.39	1	d	2.2	*cis*-<u>H</u>C=CCO

The observed rotation was $[\alpha]_D^{22}$ = +4.26° (*c* 0.19, MeOH).

Although the following factors are evident for our isolated lactone (65 B): the *downfield* shift of the methyl group in the ^{1}H n.m.r. spectrum, the relatively smaller vicinal *coupling constant* ($J_{H-3,H-4}$), its observed *optical rotation* and the fact that the compound is a *liquid*, there is no clear cut evidence for the structure of this compound.

These findings can be rationalised in terms of the following:

(1) The starting diastereomeric mixture, utilised for the lactonisation procedure, was enriched in the "minor" (*syn*) diastereomer (134 B).

(2) Under our lactonisation conditions, the *syn* isomer had lactonised to a greater extent than the *anti* isomer.

Furthermore, spectral analysis of the isolated *mixture* of lactones revealed that it was enriched with the above "*syn*" lactone (65 B). Thus, the other lactone is possibly the corresponding "*anti*" lactone (65 A), i.e., that reported by Scolastico and co-workers, which obviously exists as an enantiomeric pair. The latter assignment was supported by its n.m.r. spectral data, especially:

(1) The *upfield* shift of the methyl doublet (at 1.41 ppm), as compared with the *downfield* shift (at 1.44 ppm), for the corresponding "*syn*" lactone (65 B).
(2) The larger vicinal coupling constant ($J_{H-3,H-4}$ = 5.8 Hz) as compared with 4.4 Hz for the "*syn*" lactone.

The above assignments are further supported by application of METHODS A, B and C which were utilised earlier for assignment of stereosubstructure for the *acyclic* diastereomeric mixtures, although these lactones are obviously *cyclic* systems.

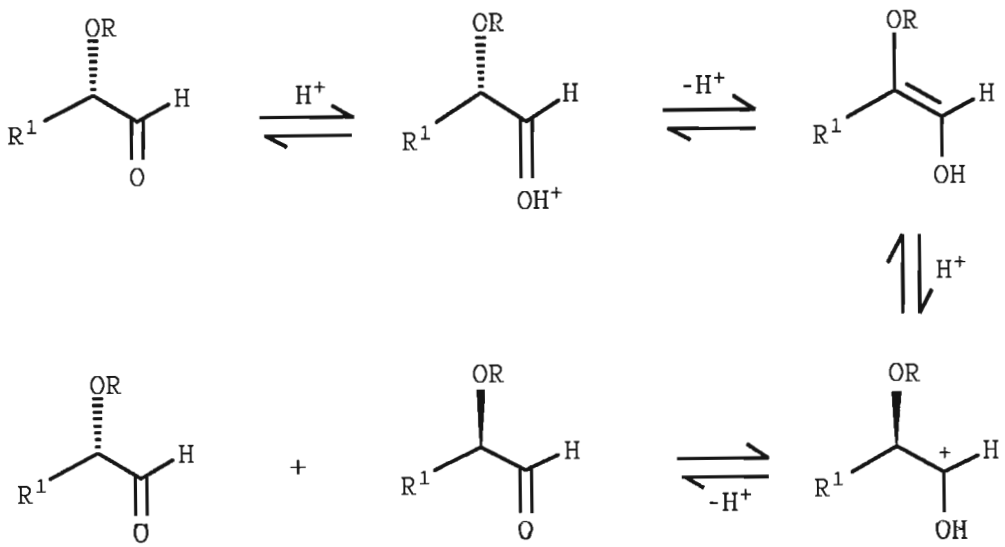
Another interesting feature in the ^1H n.m.r. spectrum of the mixture of lactones (65 A/B) is the *downfield* shift of the O*H* resonance (3.52 ppm) for the *syn* lactone (65 B), compared to the *upfield* shift (3.16 ppm) for the *anti* lactone (65 A). Thus, in this case, $\delta_{OH}(syn) > \delta_{OH}(anti)$, in accordance with the "Hoffman-Landmann rule" (METHOD D), although a *cyclic* system is the substrate.

2.6 RACEMISATION OF THE ALKOXY ALDEHYDES.

From the previous discussion, it is evident that some degree of racemisation of the optically active α-alkoxy aldehydes occurs, both during their purification (flash chromatography) and also during their reaction under the Baylis-Hillman conditions.

2.6.1 ACID-CATALYSED RACEMISATION.

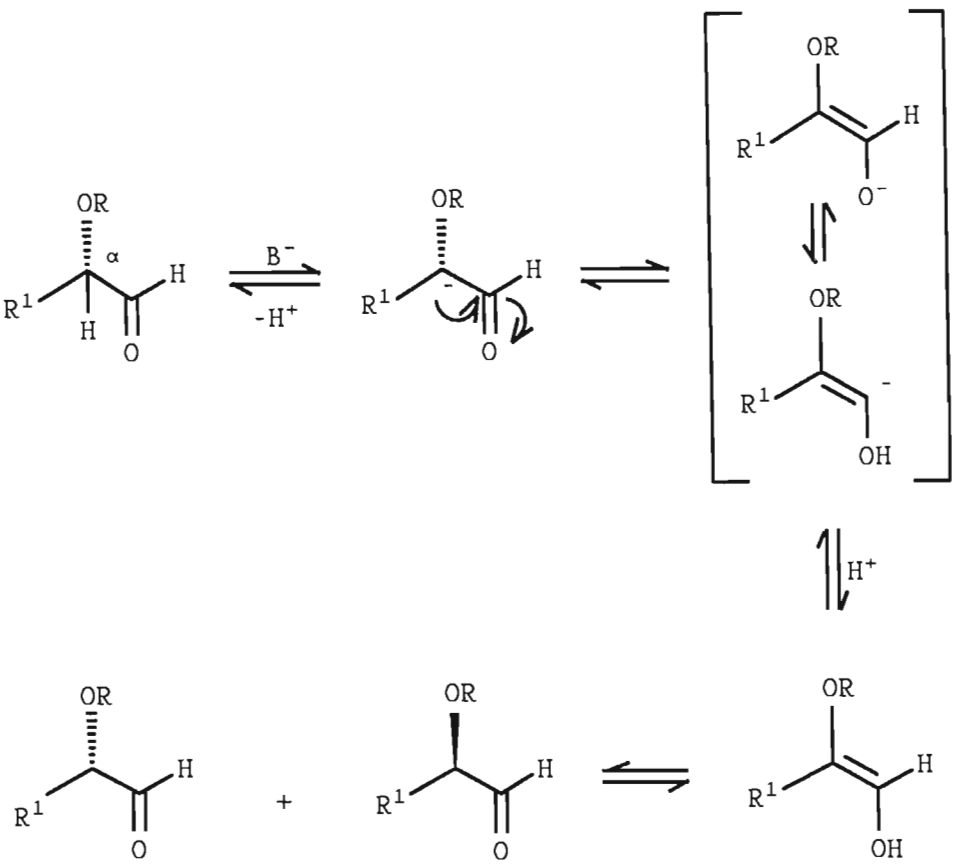
Acid-catalysed racemisation is proposed to occur via the following pathway (SCHEME 38).



SCHEME 38.

2.6.2 BASE-CATALYSED RACEMISATION.

Base-catalysed racemisation, for example, by DABCO, is proposed to occur by α-proton abstraction (SCHEME 39).



SCHEME 39.

Thus, for those compounds [(131), (132), (133), (134), (135), (64), (141), (66) and (127)] that were derived from the homochiral aldehydes [(104), (105), (20) and (115)] (TABLE 5), the diastereomeric products can be expected to be less than 100% enantiomerically pure or racemic.

CHAPTER 3

3. REACTIONS OF THE *N*-PROTECTED α-AMINO ALDEHYDES.

In view of the relative success we obtained with the various α-alkoxy aldehydes, it was of interest to examine the analogous α-chiral (or racemic) *N*-protected α-amino aldehydes under these metal-free non-coordination reaction conditions. A survey of the literature reveals that the direct addition of organometallic reagents to these compounds does not proceed with any great stereoselectivity.

A prerequisite was the preparation of some selected *N*-protected, α-amino aldehydes in optically active or racemic form.

3.1 THE AMINO ALDEHYDES.

3.1.1 PHYSICAL AND CHEMICAL PROPERTIES.

N-protected α-amino aldehydes are usually colorless solids or oils, well soluble in typical organic solvents. They are relatively unstable, particularly in solution. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. It is therefore recommended to use these compounds immediately after preparation; however, if purification is necessary, two methods are available:[48]

(1) flash chromatography on silica gel,[105] or
(2) formation of the much more stable semicarbazone,[160] followed by simple chromatography and subsequent

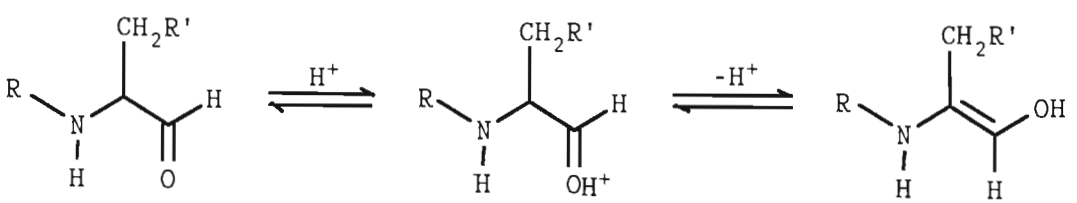
decomposition to return to the pure aldehyde.

The optical stability of some *N*-protected α-amino aldehydes during chromatography on silica gel was first studied by Ito *et al.*[161] (TABLE 22).

TABLE 22: Optical stability of selected α-amino aldehydes on silica gel.

α-AMINO ALDEHYDE	DEGREE OF RACEMISATION (%)		
	EXPOSURE TIME (h)		
	0	6	22
Cbz-*N*-nitro-(L)-argininal	0	5	9
Cbz-(L)-leucinal	0	32	65
Cbz-(L)-phenyl alaninal	0	53	85
Cbz-*S*-benzyl-(L)-cysteinal	7	99	100

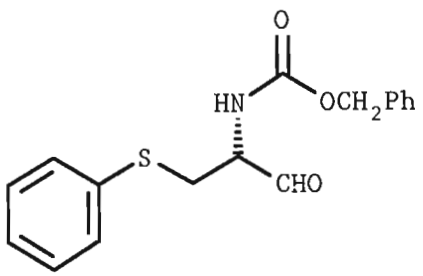
As shown in TABLE 22, the order of extent of racemisation of Cbz-α-amino aldehydes on silica gel was as follows: Cbz-(*S*)-benzyl-(L)-cysteinal >> Cbz-(L)-phenylalaninal > Cbz-(L)-leucinal >> Cbz-N^G-nitro-(L)-argininal. The authors[161] proposed a racemisation mechanism for compounds (17) involving the protonated form (170) and the enol (171) (SCHEME 40).



(17) (170) (171)

SCHEME 40.

N-protected-α-amino aldehydes (17) with an enol-stabilising R'group, e.g., Cbz-*S*-benzyl-cysteinal (172) racemise extremely quickly during contact with silica gel.



(172)

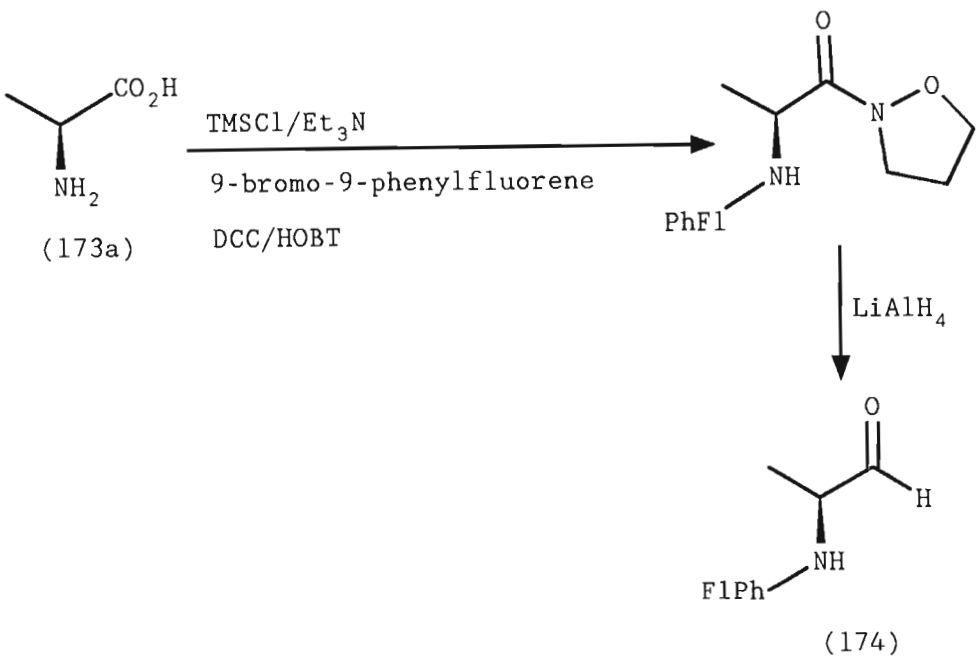
Further studies on the optical stability of *N*-protected α-amino aldehydes were carried out by Evans and co-workers.[162] They found that the reduction-oxidation procedure (BH_3.THF-CrO_3/Py) generates ^{t}Boc-α-amino aldehydes with complete retention of chiral integrity (greater than 99.5%). The optical lability of the crude aldehydes depends on their structure. Thus, as expected from previous studies, ^{t}Boc-(L)-phenylalaninal appeared to be very much less stable than ^{t}Boc-(L)-leucinal. Very illustrative results of optical stability investigations of ^{t}Boc-(L)-leucinal, during storage at various temperatures, are shown in TABLE 23.

TABLE 23: Optical stability of ^{t}Boc-(L)-leucinal during storage.

STORAGE TIME (d)	STORAGE TEMTERATURE (°C)	$[\alpha]_D^{24}$ (°)	L/D (HPLC)
0		+18.2	100
1	-30	+17.9	99/1
9	-30	+17.4	99/1
9	+24	+6.9	70/30

From these studies it was concluded that even ^{t}Boc-(L)-leucinal, subjected to any prolonged regimen including drying, could no longer be regarded as being optically pure unless verified as such.[162]

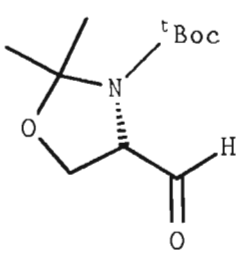
Two additional important reports on the configurational stability of *N*-protected α-amino aldehydes have appeared. Lubell and Rapoport[163] describe the synthesis of *N*-[9-(phenylfluorenyl]-(L)-alaninal (174) from (L)-alanine (173a) (SCHEME 41).



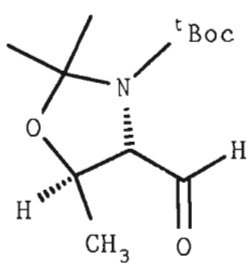
SCHEME 41.

Exposure to silica gel or to a non-nucleophilic base caused no detectable racemisation. The phenylfluorenyl *N*-protecting group also maintains the configurational integrity of (L)-alaninal during C-C bond-forming reactions, affording enantiomericallly pure products from Wittig reactions, aldol condensations and Grignard additions.[163]

The second report, by Garner and Park,[164] describes the synthesis of *N*, *O*-di-protected (L)-serinal (175a) and (L)-threoninal (176) (FIGURE 49).



(175a)



(176)

FIGURE 49.

These differentially protected β-hydroxy α-amino aldehydes were produced in a 93-95% enantiomeric excess. The configurational stability of these compounds during their purification, either by vacuum distillation or by flash chromatography, was also demonstrated.[164]

3.1.2 PREPARATIVE ROUTES.

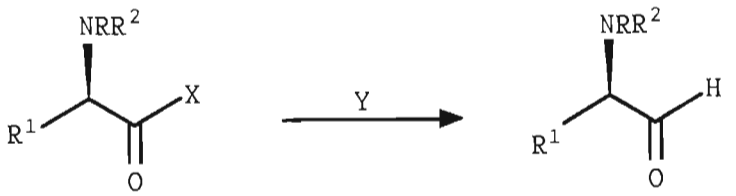
Literature methods will be reviewed briefly.

3.1.2.1 REDUCTIVE METHODS.

The main source of α-amino aldehydes are the readily accessible α-amino acids. Only on occasion are these aldehydes obtained from other chiral precursors. Usually,

the synthetic route proceeds *via* esters or active amides of α-amino acids which are finally reduced. A second approach is based on the oxidation of α-amino alcohols obtained from α-amino acids.

Procedures based on reduction of esters or active amides (177) have been reported[48] (SCHEME 42).

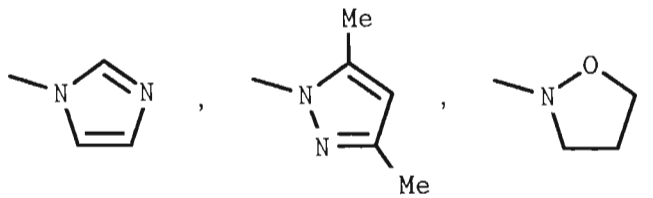


(177) (17)

R = H

R^2 = Cbz, ^{t}Bu, PhFl, Ac, Pht

X = OMe, OEt, N(OMe)Me,

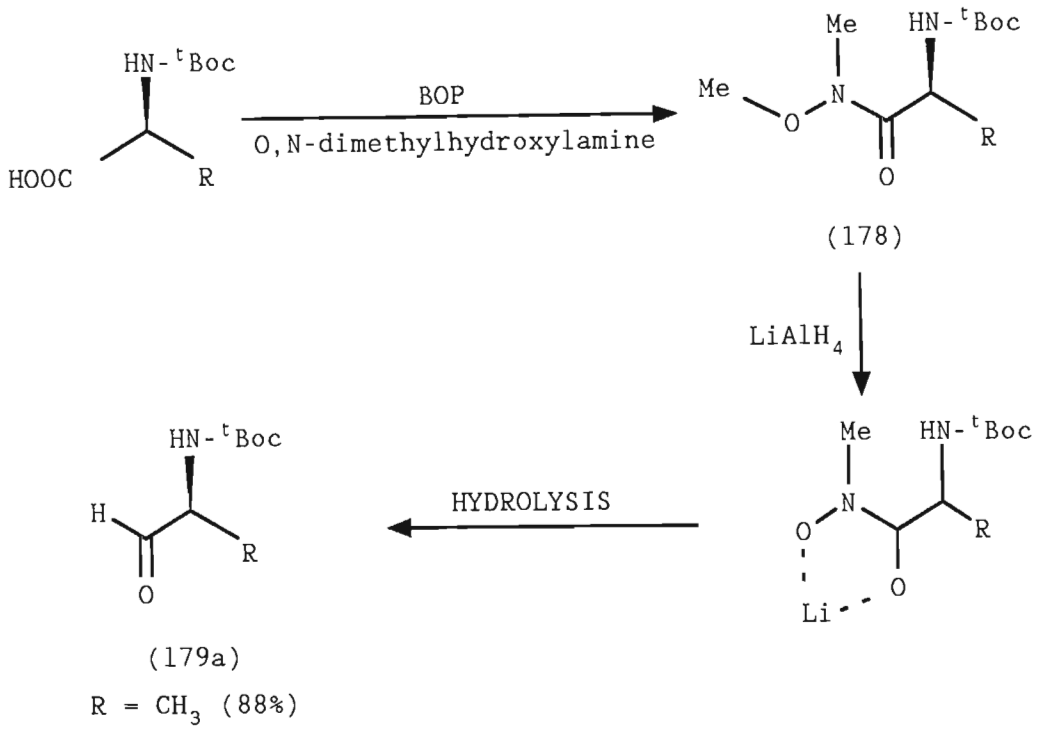


Y = DIBAL-H, $LiAlH_4$, H_2/Pd-C

SCHEME 42.

An efficient method, which affords these aldehydes without racemisation and overreduction, has been reported by Fehrentz and Castro.[165] The preparation of the ^{t}Boc-α-amino aldehydes, e.g., (179a), is based on reduction of *N*-methoxy-*N*-methyl carboxamides (178) with lithium aluminium hydride, which proceeds through the stable lithium-chelated intermediate; further reduction is precluded by intramolecular

complexation (SCHEME 43).

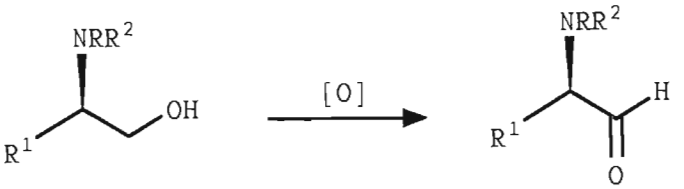


SCHEME 43.

Similar results were found by Lubell and Rapoport[163] during reduction of the respective isoxazolides.

3.1.2.2 OXIDATIVE METHODS.

Procedures based on oxidation of *N*-protected α-amino alcohols (180) have also been reported[48] (SCHEME 44).



(180) (17)

R = H, Bz

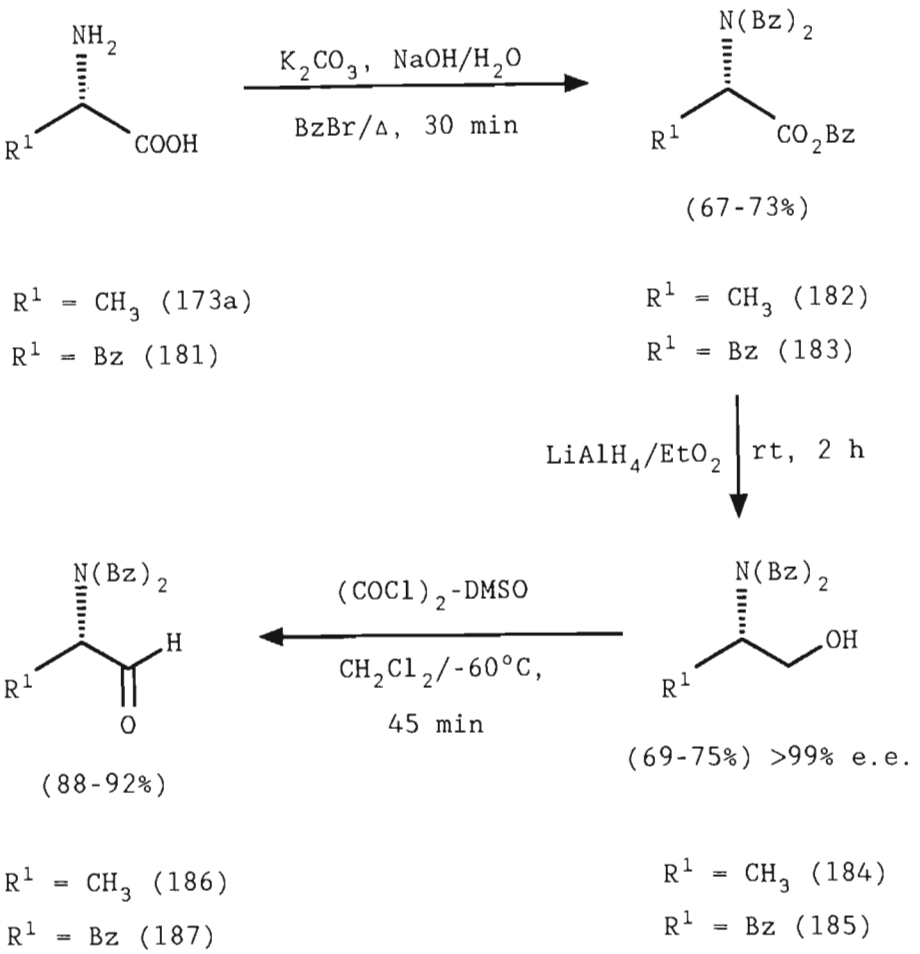
R/R^2 = Pht

[O] = CrO_3/Py, DMSO(SO_3.Py), DMSO/$(COCl)_2$, DMSO/TFAA, DMSO/DCC, PCC and PDC.

SCHEME 44.

The *N*-protected α-amino alcohols (180) are best obtained by borane-THF reduction of *N*-protected α-amino acids[166a] or by $NaBH_4$-LiCl[166b] or $NaBH_4$-$CaCl_2$[166c] reduction of the corresponding methyl ester.

Reetz *et al.*[167] showed that the *N*,*N*-dibenzylated α-amino aldehydes, e.g., (186) and (187), are readily accessible by the following procedure (SCHEME 45).

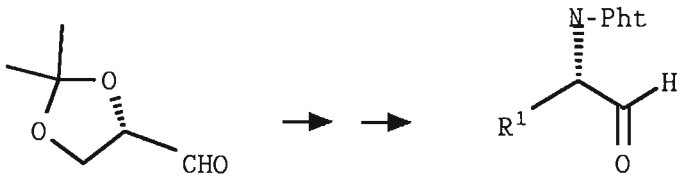


SCHEME 45.

More recently, however, Hung *et al.*[168] found that ozonolysis of olefinic precursors generally provided the most convenient route to the α-amino aldehydes.

3.1.2.3 MISCELLANEOUS METHODS.

A convenient and elegant synthesis of five phthaloyl-(L)-α-amino aldehydes, e.g. (188a), starting from 2,3-*O*-isopropylidene-(D)-glyceraldehyde (20), was described by Mulzer *et al.*[169] (EQUATION 41).

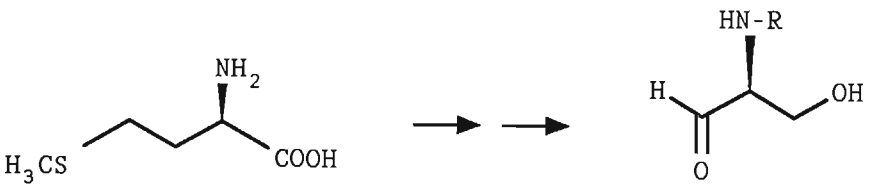


(20) (188a)

$R^1 = CH_3$

EQUATION 41.

Ohfune and Kurokawa[170] described a practical method for the synthesis of *N*-protected serinal (189) in both enantiomeric forms from (L)- or (D)-methionine (EQUATION 42).

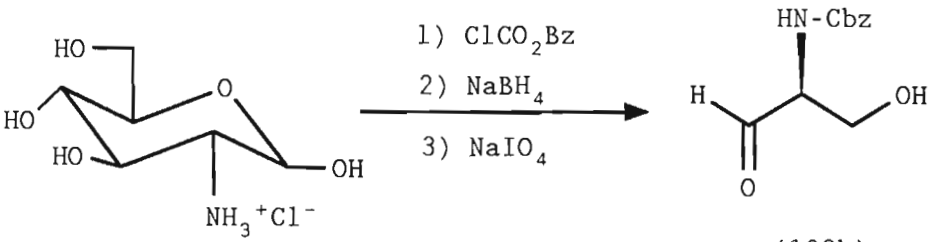


R = ^{t}Boc (189a)

R = Cbz (189b)

EQUATION 42.

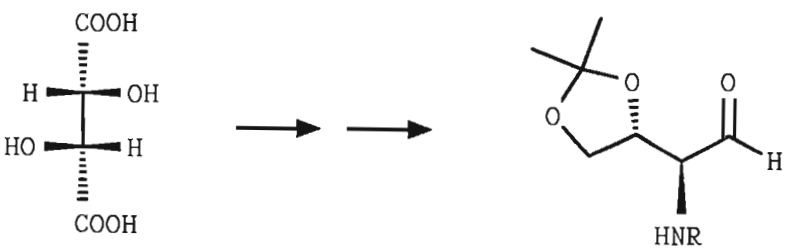
Recently, a new method for preparation of *N*-Cbz-(L)-serinal (189b), based on sodium periodate oxidation of suitably protected (D)-glucosamine, was reported by Münster *et al.*[171] (EQUATION 43).



(189b)

EQUATION 43.

Another example of the synthesis of chiral β-hydroxy-α-amino aldehydes (190), starting from (L)- and (D)-tartaric acid, was described by Saito *et al.*[172] (EQUATION 44).



R = ^{t}Boc, Cbz

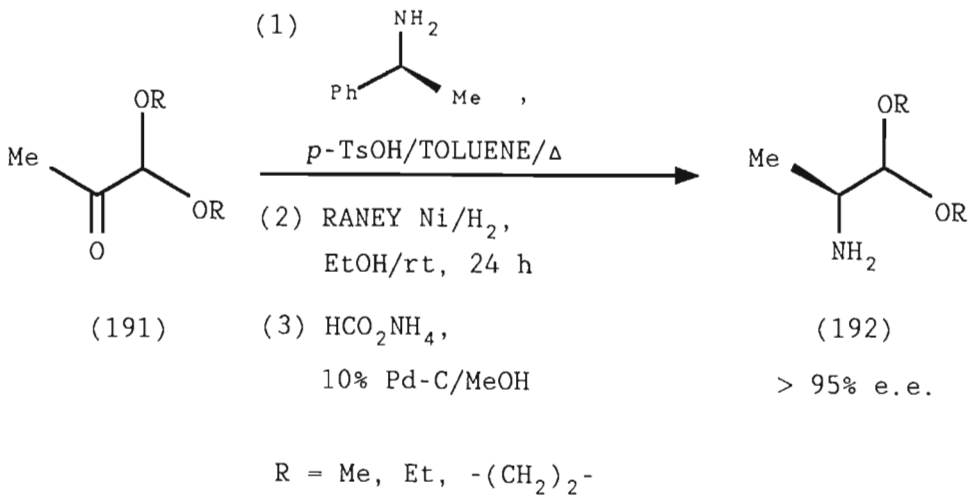
(190)

EQUATION 44.

For the preparation of the carbonyl-protected alanine-derived amino aldehydes (192), the additional acetalization of the configurationally labile aldehydes and subsequent

N-protection is required. Apart from these synthetic difficulties and the number of steps required, a further disadvantage of such conventional α-amino aldehyde acetal syntheses results from the limitation that only amino acid precursors with (L)-configuration are easily accessible from the chiral "pool".[4]

Bringmann and Geisler[173] report a simple, useful method for the reliable preparation of configurationally stable, enantiomerically pure alanine-derived α-amino acetals (192), by asymmetric (catalytic) reduction of chiral imines, prepared from the α-oxo acetals (191) (SCHEME 46).



SCHEME 46.

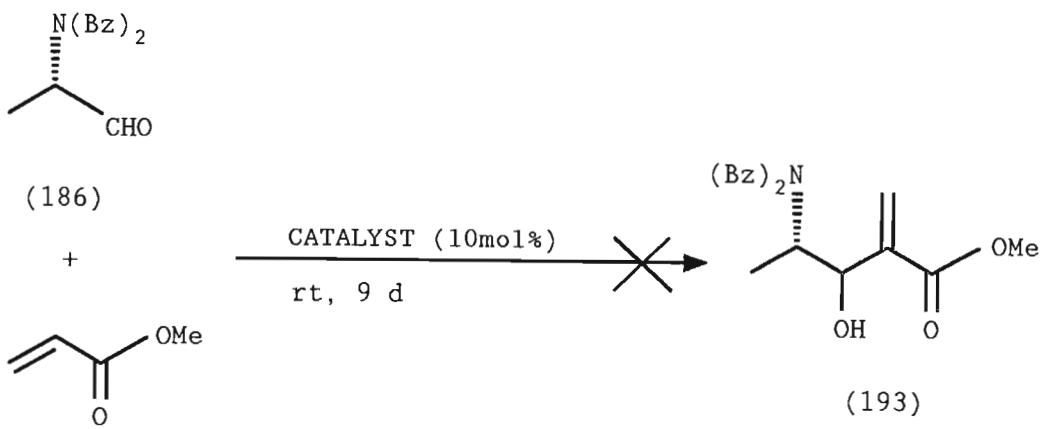
3.1.2.4 PREPARATION (AND INITIAL REACTION).

Initial attention was directed to the report by Reetz *et al.*,[167] who reported preparation of the *N*,*N*-dibenzylamino aldehydes in three steps from readily available starting materials, viz., the chiral "pool"[4] of (L)-α-amino acids (SCHEME 45). These compounds were claimed to be configur-

ationally stable and more easily handled than their *N*-^{t}Boc-protected analogues.

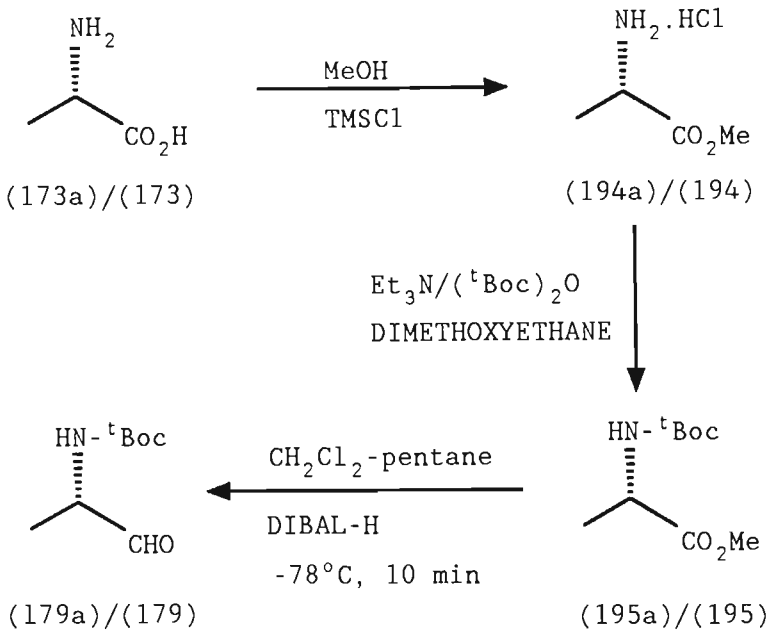
Thus, (S)-2-(*N*,*N*-dibenzylamino)propanal (186) and (S)-2-(*N*,*N*-dibenzylamino)-3-phenylpropanal (187), derived from (L)-alanine (173a) and (L)-phenylalanine (181) respectively, were prepared via reduction of the corresponding esters (182) and (183) to the alcohols (184) and (185) followed by Swern[97] oxidation of the latter to the optically active *N*-protected α-amino aldehydes (SCHEME 45).[167]

However, the coupling reaction of (186) with methyl acrylate, utilising 10 mol% of (±)-3-quinuclidinol (71) as catalyst, did not proceed at all. Although ^{1}H n.m.r. of the reaction mixture indicated disappearance of the aldehyde proton (possibly by decomposition) after nine days, subsequent workup did not afford the desired or expected β-hydroxy-γ-amino-ester (193) (EQUATION 45).



EQUATION 45.

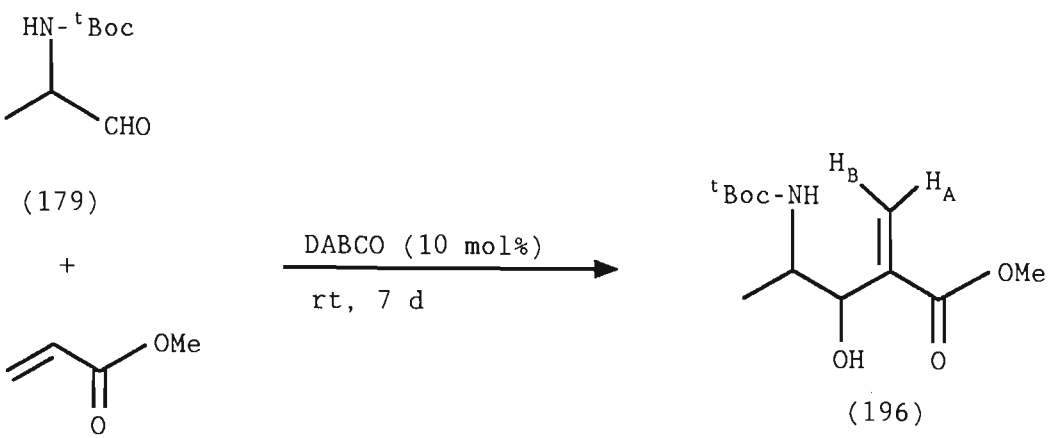
It was then decided to synthesise the ^{t}Boc-protected amino aldehyde, viz., (±)-2-[(*tert*-butyloxy)-carbonyl-amino]-propanal (179) by a known route[174] (SCHEME 47).



SCHEME 47.

(DL)-Alanine (173) was protected as the methyl ester (194). The resulting hydrochloride (194) was protected using di-*tert*-butyl dicarbonate and afforded (±)-methyl 2-{[(*tert*-butyloxy)carbonyl]amino}propanoate (195). DIBAL-H reduction of (195) afforded the racemic aldehyde (179).

Its subsequent reaction in the Baylis-Hillman reaction was promising even though 10 mol% of catalyst was used (EQUATION 46).

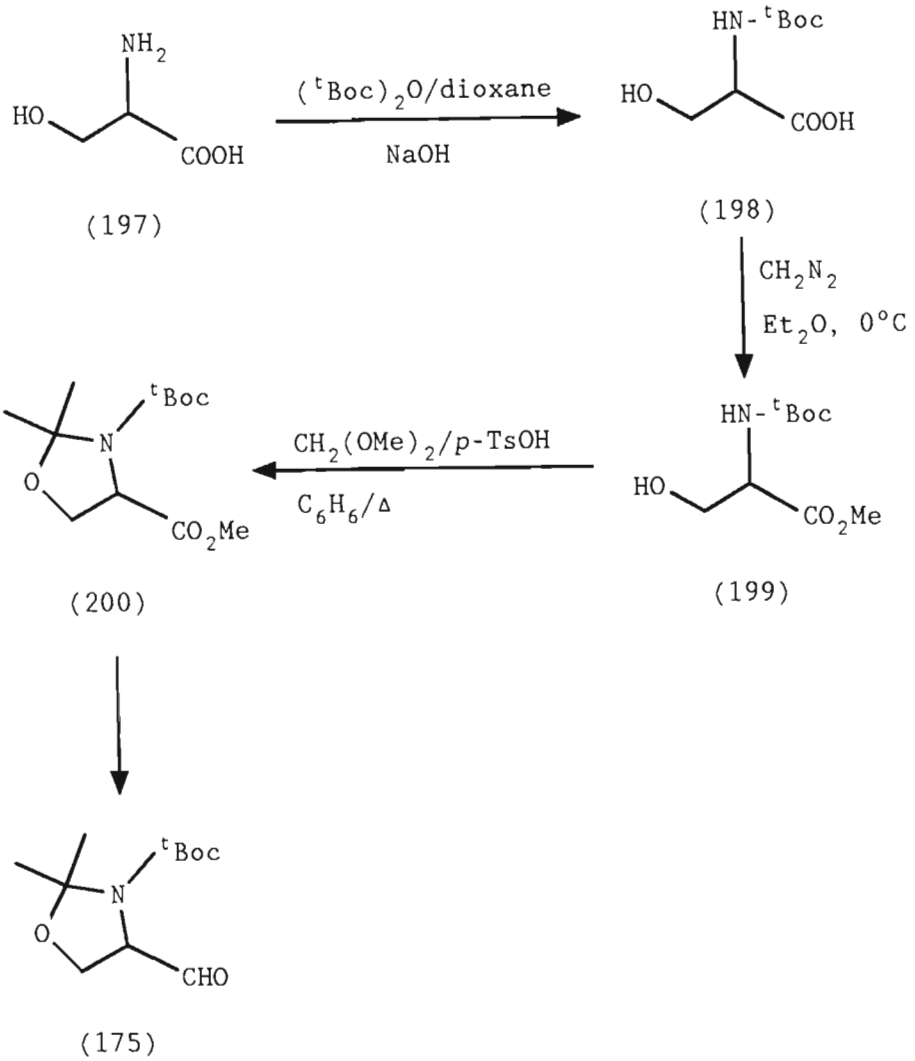


EQUATION 46.

Proof that the desired product (196) was obtained, was evident from the presence of the characteristic peaks for the vinyl protons (H_A and H_B) in the ^1H n.m.r. spectrum, (viz., δ/5.9-6.4 ppm) of the crude reaction product (196). The optically active aldehyde (179a), derived from (L)-alanine (173a), was then prepared as outlined in (SCHEME 47).

A study was then primarily directed at establishing the influence of the choice of *N*-protection on the overall reactivity of the aldehyde and also on the diastereoselectivity of the coupling reaction. Thus, in addition to aldehydes (179), (186) and (187), the cyclic serine-derived oxazolidinone aldehyde (175), the cyclic proline-derived aldehyde (204), and the alanine-derived aldehydes (188) and (212) were also prepared.

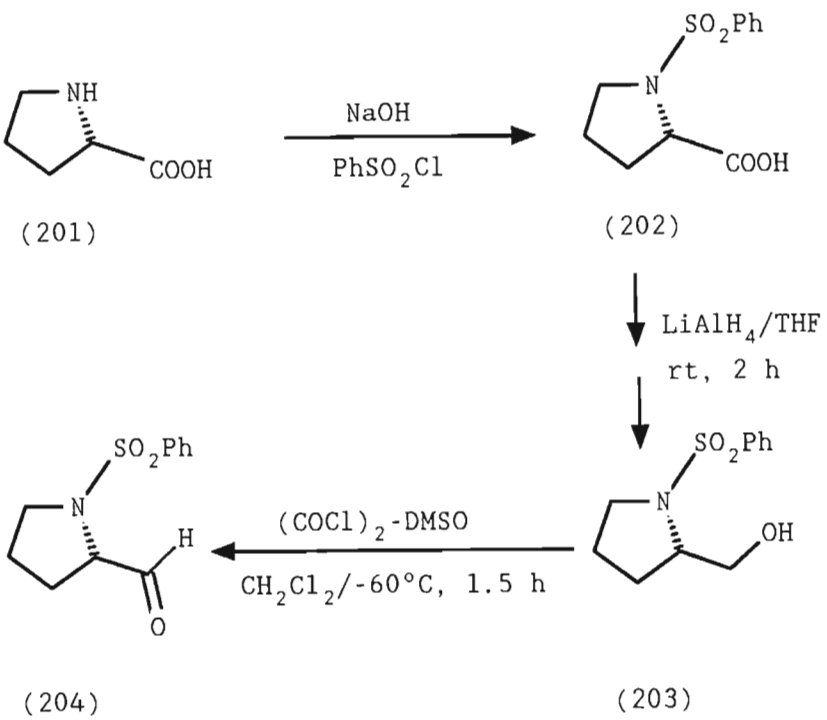
Synthesis of the aldehyde (175) was based on the report by Garner and Park[164], who showed that the oxazolidine aldehydes (175a) and (176) (FIGURE 49), may be conveniently prepared and purified on a synthetically useful scale from commercially available serine and threonine derivatives (SCHEME 48).



SCHEME 48.

Treatment of the free amino acid (DL)-serine (197) with di-*tert*-butyl dicarbonate, at pH ≥ 10, followed by esterification of the crude product (198) with diazomethane afforded the *N*-^{t}Boc methyl ester (199). Protection of the remaining O-H and CON-H functionalities was achieved by slow distillation from a solution made up of (199), dimethoxypropane and a catalytic amount of *p*-toluenesulphonic acid. This afforded the oxazolidine ester (200). Subsequent reduction of (200) to the corresponding aldehyde (175) was effected with DIBAL-H.

The synthesis of the (S)-(*N*-phenylsulfonyl)prolinal (204) is outlined in SCHEME 49.



(201) (202) (203) (204)

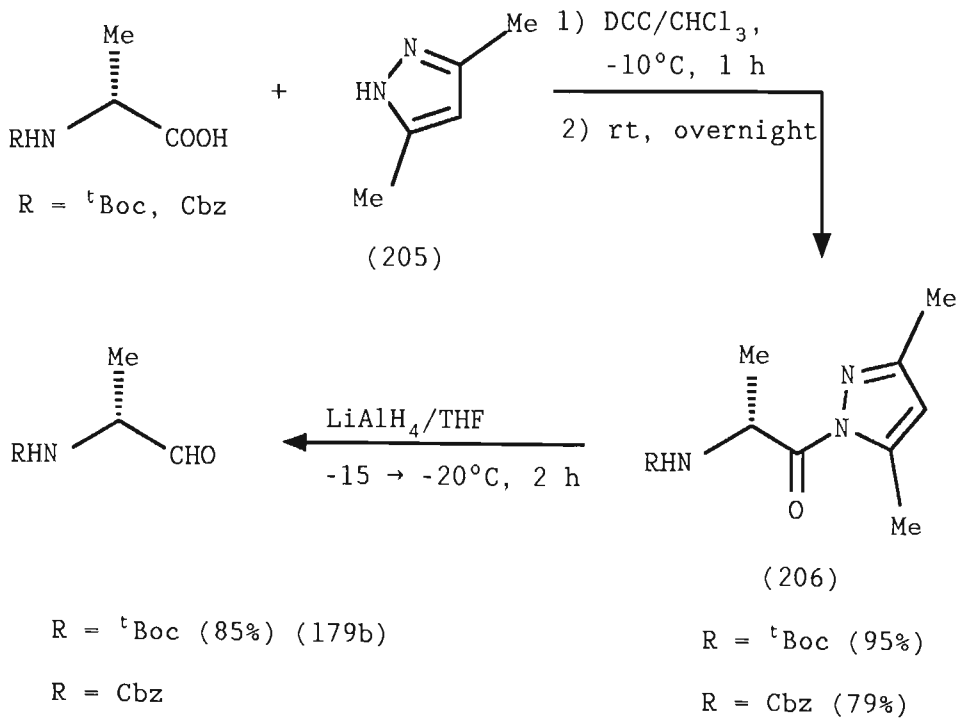
SCHEME 49.

N-Phenylsulfonyl proline (202) was prepared from (L)-proline (201) via benzenesulfonyl chloride protection.[175] Standard lithium aluminium hydride reduction of the acid (202) to the alcohol (203), followed by Swern[97] oxidation, afforded the aldehyde (204). Purification was effected by flash chromatography.[105]

Diisobutylaluminium hydride (DIBAL-H) reduction of methyl, or ethyl esters is often accompanied by some overreduction to the respective alcohols.[48] The same remarks apply to lithium aluminium hydride reduction of imidazolides. However, the reduction of 3,5-dimethylpyrazolides (206), is

apparently free from overreduction.[48]

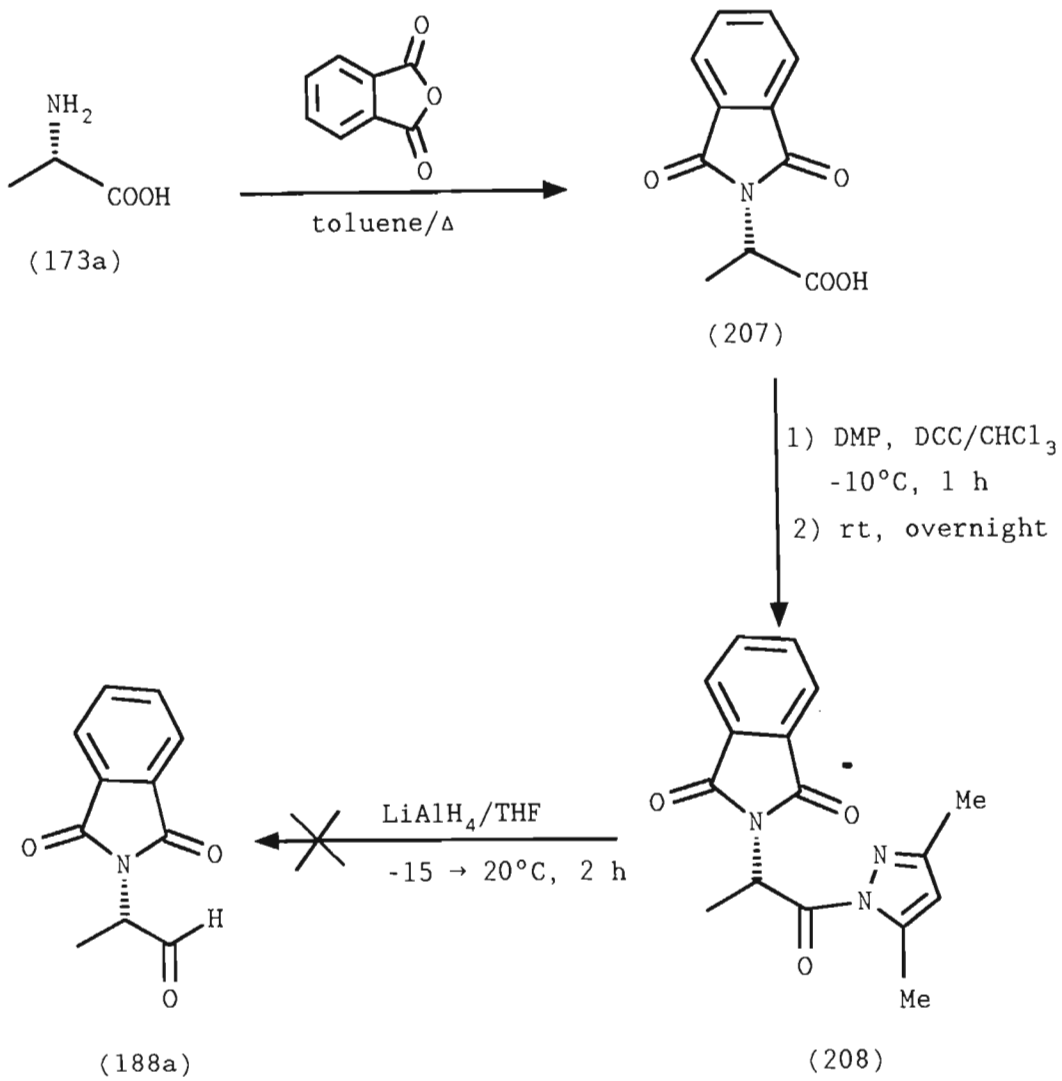
Initial efforts towards the synthesis of the phthaloyl-protected amino aldehyde (188a) were based on a report by Ohno and co-workers,[176] who required chiral amino aldehyde precursors in their studies toward the synthesis of Bleomycin.[176] They converted (D)-alanine derivatives to the chiral (R)-amino aldehydes, for example, (179b), by first preparing 3,5-dimethylpyrazoles[177] (206) followed by reduction under mild conditions with lithium aluminium hydride[177] (SCHEME 50).



SCHEME 50.

Thus, treatment of (L)-alanine with phthalic anhydride in refluxing toluene[178] afforded the *N*-protected amino acid

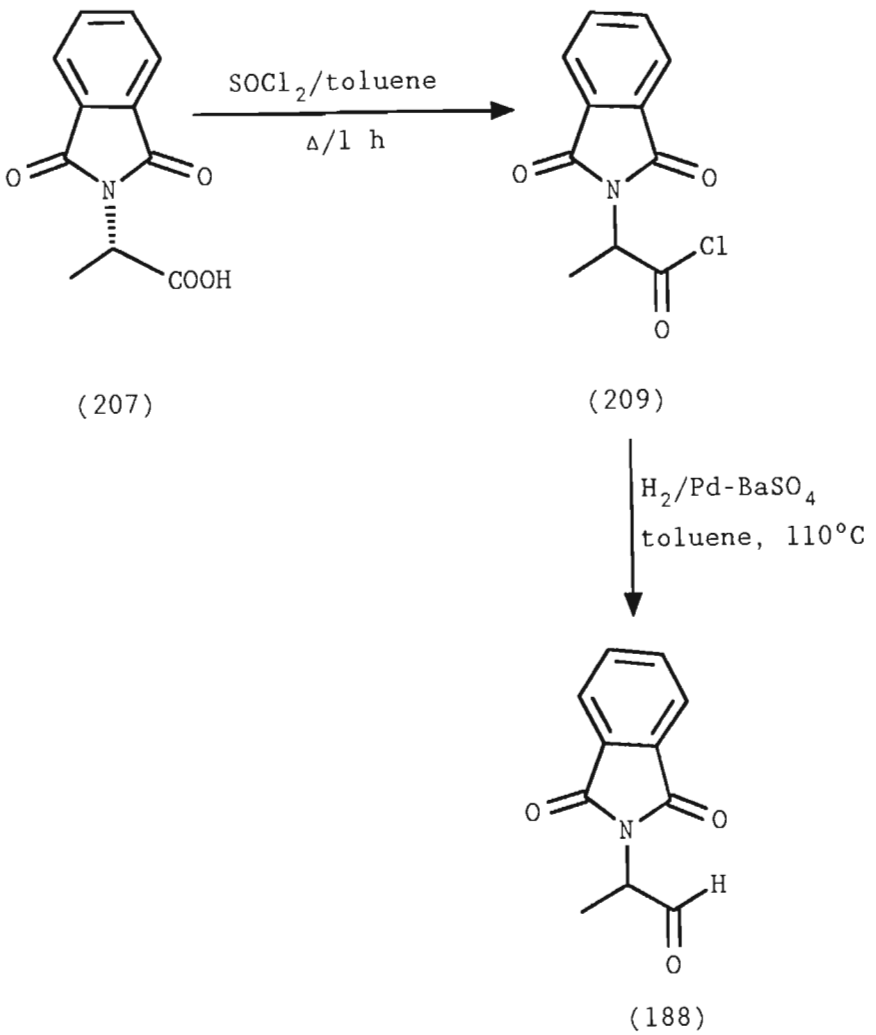
(207) (SCHEME 51).



SCHEME 51.

Subsequent conversion of the acid to the 3,5-dimethyl-pyrazole derivative (208) proceeded with success. However, an attempted reduction[177] of (208) to the corresponding aldehyde (188a) resulted in isolation of some unknown polymeric material, which was found to be insoluble in most solvents. The above route was therefore abandoned.

The desired aldehyde (188) was eventually prepared by a known route[179] (SCHEME 52).



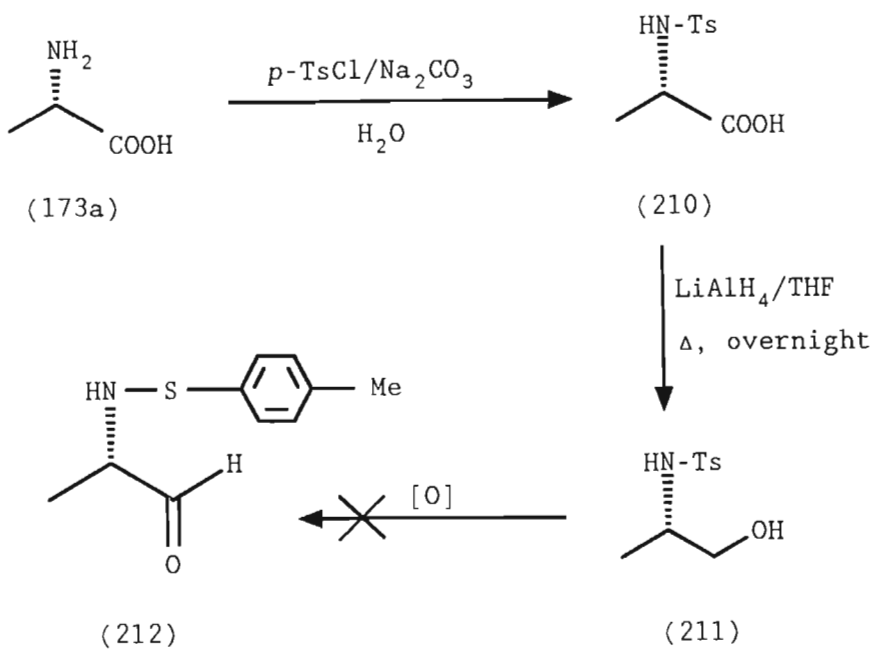
(207) (209) (188)

SCHEME 52.

The protected acid (207) was first converted to the corresponding acid chloride (209) with thionyl chloride. However, it was noted at this stage that the acid chloride was optically inactive. Nevertheless, we proceeded with the synthesis. Subsequent Rosenmund reduction[180] of the acid chloride gave the *N*-protected amino aldehyde (188) in

racemic form. The crude aldehyde was utilised without further purification.

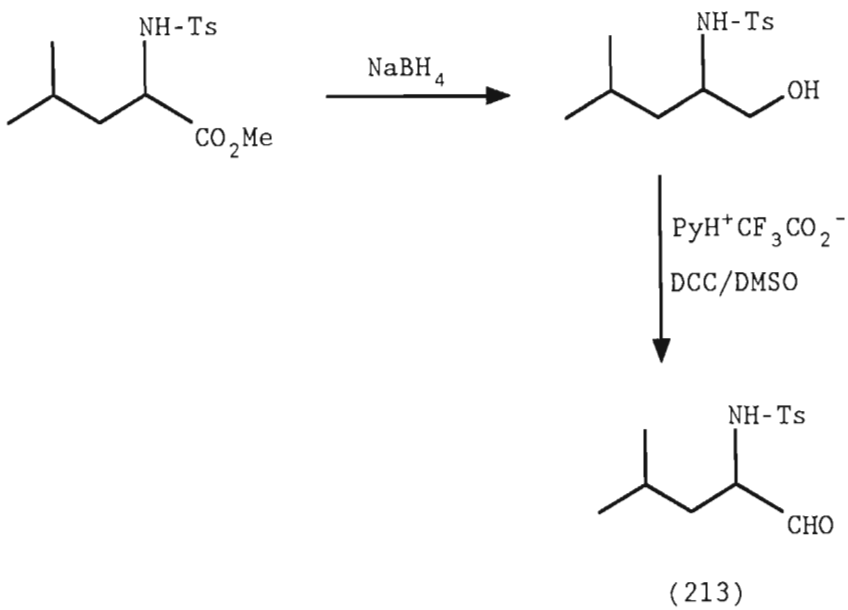
Preparation of the *N*-tosyl-protected alaninal (212) turned out to be extremely difficult by standard procedures. The following route was initially attempted (SCHEME 53).



SCHEME 53.

N-Tosyl-(L)-alanine (210) was prepared from (L)-alanine (173a) according to the known procedure.[175] The *N*-protected acid (210) was then reduced to the corresponding alcohol (211). Oxidation of (211) was attemped with a variety of oxidising systems.

Szelke *et al.*[181] reported the synthesis of an α-*N*-tosyl amino aldehyde (213) by a sulfoxide-carbodiimide oxidation[182] reaction of an alcohol (SCHEME 54).

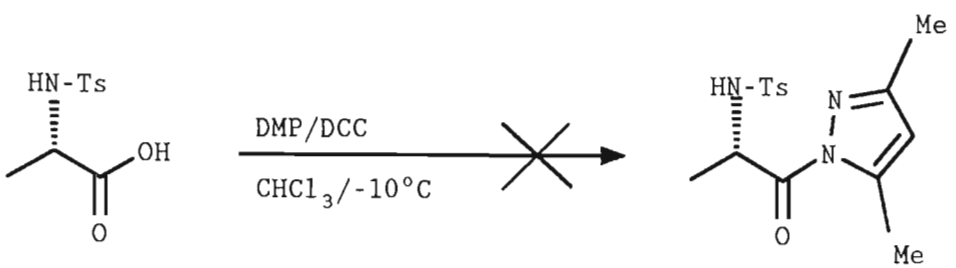


(213)

SCHEME 54.

However, oxidation of the alcohol (211) under these conditions,[182] led only to the recovery of the starting amino alcohol (211). In addition, the Swern[97] oxidation, (oxalyl chloride-DMSO), lead tetraacetate, sodium periodate[116] and PCC[94] oxidation reagents all failed to furnish the desired aldehyde (212). In most cases, only the starting alcohol was recovered after the workup procedure.

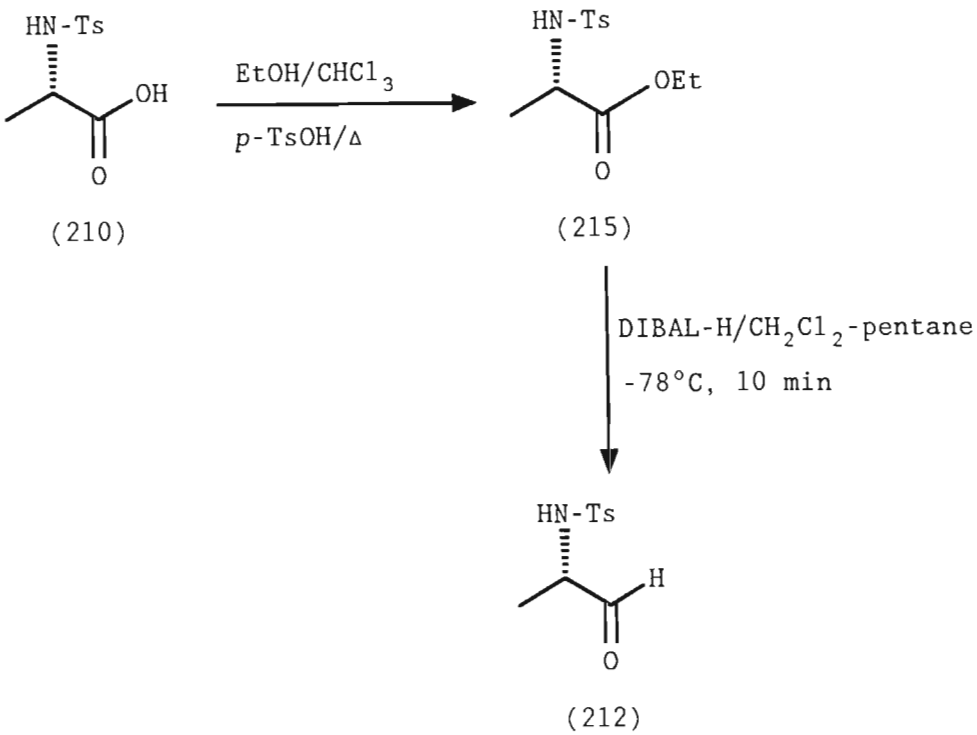
An attempted conversion of the *N*-protected amino acid (210) to the 3,5-dimethyl pyrazole derivative (214) led to a complex mixture of unidentifiable compounds (EQUATION 47).



(210) (214)

EQUATION 47.

Eventually, the following procedure (SCHEME 55) afforded the target molecule (212). However, some starting ester (215) was also detected by n.m.r. spectroscopy and GC/MS (SCHEME 55).

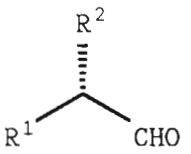


SCHEME 55.

The ethyl ester (215) was prepared by refluxing a mixture of the *N*-protected amino acid (210) in ethanol/chloroform.[183] Subsequent reduction of (215) with DIBAL-H afforded the amino aldehyde (212).

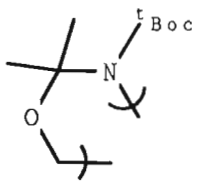
The aldehyde was also found to be unstable to silica gel during flash chromatography and was used without further purification.

TABLE 24 summarises the data for the various *N*-protected α-amino aldehydes (85).



(85)

TABLE 24: Synthesis of the *N*-protected α-amino aldehydes.

ALDEHYDE	R^1	R^2	$[\alpha]_D^{21-30}$ (CH_2Cl_2)	CONFIGURATION	YIELD[c] (%)
186	Me	$N(Bz)_2$	-34.1[a]	S	74
187	Bz	$N(Bz)_2$	-73.55	S	87
179a	Me	HN-^{t}Boc	+34.7	S	53
188	Me	N-Pht	-	±	65[d]
212	Me	HN-Ts	-[b]	S	98
204	—$(CH_2)_4$-N(SO$_2$Ph)-		-164.86	R	55
175			-	±	31

[a]Determined on the crude compound.

[b]Was not determined.

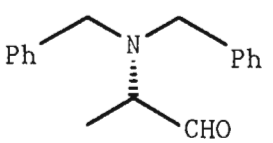
[c]Isolated yields after purification, except for aldehydes (186) and (212).

[d]Literature-reported[179] yield when purified by recrystallisation.

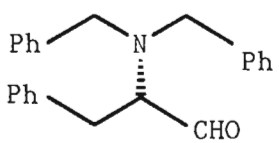
Drewes[174] reported preparation of the aldehyde (186) (TABLE 24) which was also unstable to chromatography. However, no optical rotation was reported on the crude aldehyde.

Furthermore, aldehyde (187) has a reported[174] optical rotation of $[\alpha]_D^{20}$ = -89.9° (*c* 1.88, CH_2Cl_2). The lower value obtained by us can be attributed to its racemisation during silica gel purification.

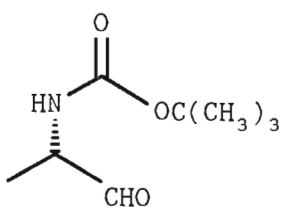
3.1.3 REACTIONS WITH METHYL ACRYLATE.



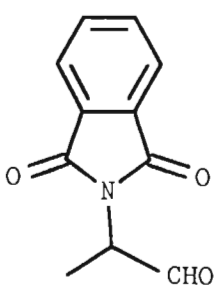
(186)



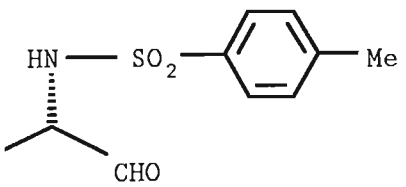
(187)



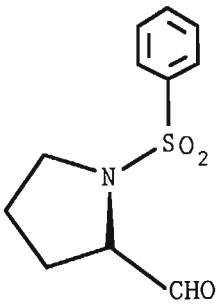
(179a)



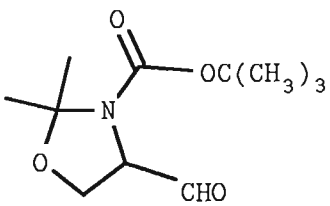
(188)



(212)



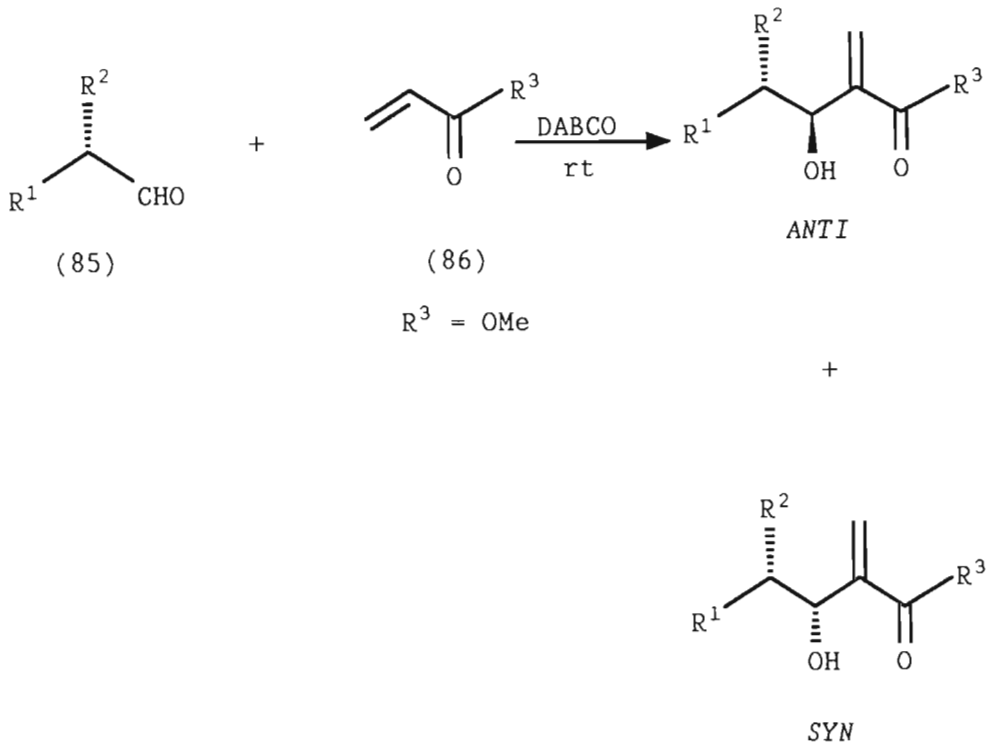
(204)



(175)

FIGURE 50.

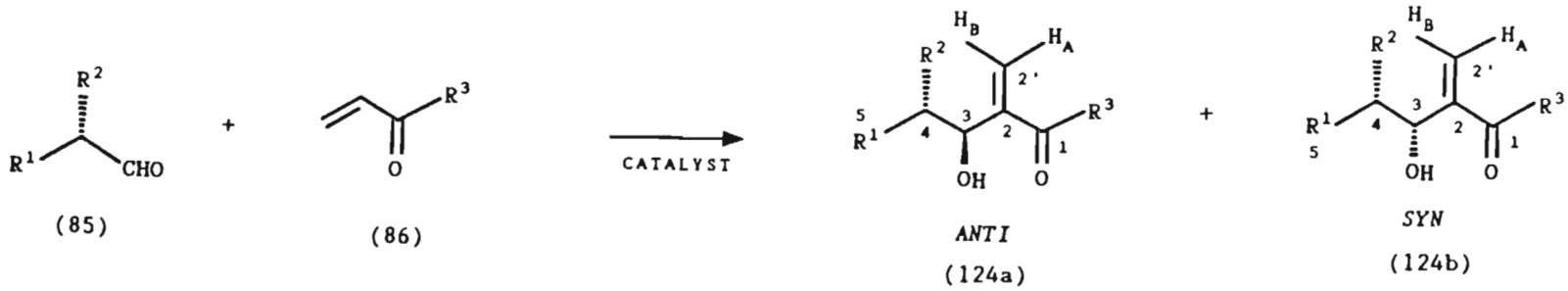
Coupling of the amino aldehydes (FIGURE 50) was carried out with an excess of methyl acrylate using molar equivalents of catalyst to obtain synthetically more useful reaction times, following our own observations[140] and also a recent publication by Basavaiah *et al.*[89] (EQUATION 18).



EQUATION 18.

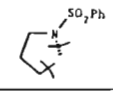
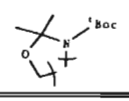
3.1.3.1 RESULTS.

The following results concerning the diastereoselectivity, were obtained (TABLE 25).



EQUATION 18.

TABLE 25: Asymmetric induction in the reactions of the *N*-protected α-amino aldehydes with methyl acrylate.

ENTRY	ALDEHYDE[a] (mmol)	R^1	R^2	R^3	CATALYST[b] (mole %)[c]	REACTION TIME (d)	COMPOUND	ANTI : SYN[d] RATIO	d.e. (%)	YIELD[e] (%)
1	186 (1.50)	Me	$N(Bz)_2$	OMe	D (10)	9	-	-	-	-[f]
2	186 (22.33)	Me	$N(Bz)_2$	OMe	Q (100)	20	193	72 : 28	44	71
3	187 (18.95)	Bz	$N(Bz)_2$	OMe	D (100)	31	216	67 : 33	34	80
4	179 (34.42)	Me	HN-^{t}Boc	OMe	D (10)	7	196	26 : 74	48	80
5	179a (12.26)	Me	HN-^{t}Boc	OMe	D (100)	<1.5	196	29 : 71	42	76
6	188 (43.15)	Me	N-Pht	OMe	D (100)	3.5	217	46 : 54	8	28
7	212 (23.30)	Me	HN-Ts	OMe	D (100)	<6	218	44 : 56	12	68
8	204 (15.60)			OMe	D (100)	<0.5	219	87 : 13	74	55
9	175 (3.06)			OMe	D (100)	<11	220	89 : 11	78	43

[a]Aldehydes in ENTRIES 4, 6 and 9 were racemic.
Aldehydes in ENTRIES 1, 2, 4, 5, 6 and 7 were reacted in crude form. However, mmol refers to the purified substrate.

[b]D = DABCO (56)
Q = (±)-3-quinuclidinol (71)

[c]Based on aldehyde.

[d]Assignments were based on previously described methods. These will be discussed in *Section 3.1.3.2.4.*

[e]Refers to isolated yield after flash chromatography, except for ENTRY 7, which represents the crude yield.

[f]No product was detected after nine days.

3.1.3.2. DISCUSSION.

3.1.3.2.1 REACTION RATE.

The pattern of aldehyde reactivity was as anticipated, with those aldehydes having electron-withdrawing *N*-protection (ENTRIES 4-8) (TABLE 25) showing greater reactivity, as opposed to those aldehydes in ENTRIES 1-3. Although the "cyclic" aldehyde (175) has the ^{t}Boc-protecting group, its observed reaction time does not follow the trend as observed the other amino aldehydes with similar electron-withdrawing *N*-protecting groups (ENTRIES 9 vs 4-8).

3.1.3.2.2 DIASTEREOSELECTIVITY.

Regarding the observed stereochemical outcome of the coupling reaction (TABLE 25), it is evident that the

diastereoselectivity is dependent on the *type* of amino group protection.

Thus, the *anti* diastereoselectivity observed for the aldehydes (186), (187), (204) and (175) (ENTRIES 2, 3, 8 and 9) is consistent with the non-chelate "Felkin-Anh"[30,33] model for diastereoselection (FIGURE 51) and is in line with the dominant stereochemical outcome observed in reactions with the chiral α-alkoxy aldehydes (CHAPTER 2).

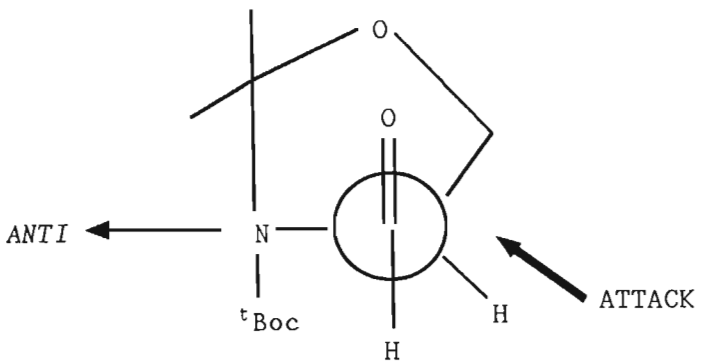
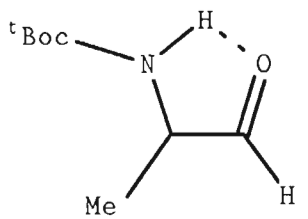


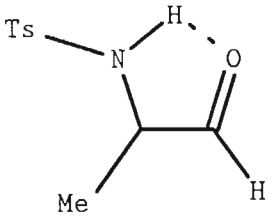
FIGURE 51.

It is also evident that the more sterically demanding cyclic proline and serine-derived amino aldehydes (204) and (175) (ENTRIES 8 and 9) lead to the best (*anti*) diastereoselectivity. This degree of induction is also superior to that observed with the analogous alkoxy aldehydes (TABLE 5) (CHAPTER 2)

The reversal of diastereoselectivity observed with the mono-protected, N*H*-^{t}Boc-protected amino aldehyde (179a) (179) and the N*H*-tosyl-protected amino aldehyde (212) (*syn* addition) is probably due to involvement of the hydrogen-bonded structures (221 A) and (221 B) (FIGURE 52).



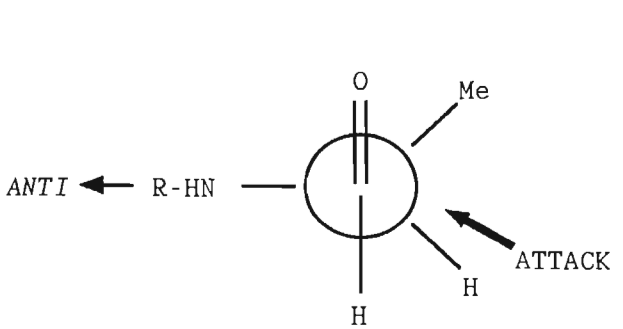
(221 A)



(221 B)

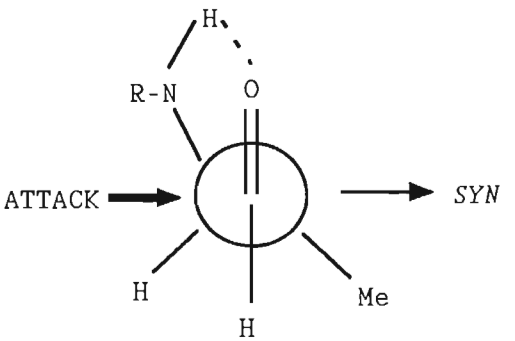
FIGURE 52.

This reversal of diastereoselectivity is in accordance with earlier reports,[52] where a proton-bridged Cram "cyclic" model[26] is thought to account for the *syn* stereochemical outcome (FIGURE 53).



"FELKIN-ANH"

(MINOR)



CRAM "CYCLIC"

(MAJOR)

R = tBoc, Ts

FIGURE 53.

A decrease in *syn* diastereoselectivity, (higher *anti* selectivity), is evident with the tosyl-protected amino aldehyde (212), as compared with the ^{t}Boc-protected amino aldehyde (179). This observation could possibly be rationalised in terms of the relative acidities of the N*H*-proton in these two aldehydes and/or the steric interactions in the transition states. The latter can be expected to be more significant for the aldehyde (212), where the presence of the somewhat more bulkier *p*-toluenesulfonyl group plays some role in destabilising this "cyclic" transition state, and thus leading to higher *anti* selectivity for this aldehyde (212).

Thus, with aldehyde (212), reaction proceeds to a greater extent through the more favourable "Felkin-Anh" conformer, as compared with the *N*H-^{t}Boc amino aldehyde (179a)/(179) (FIGURE 54).

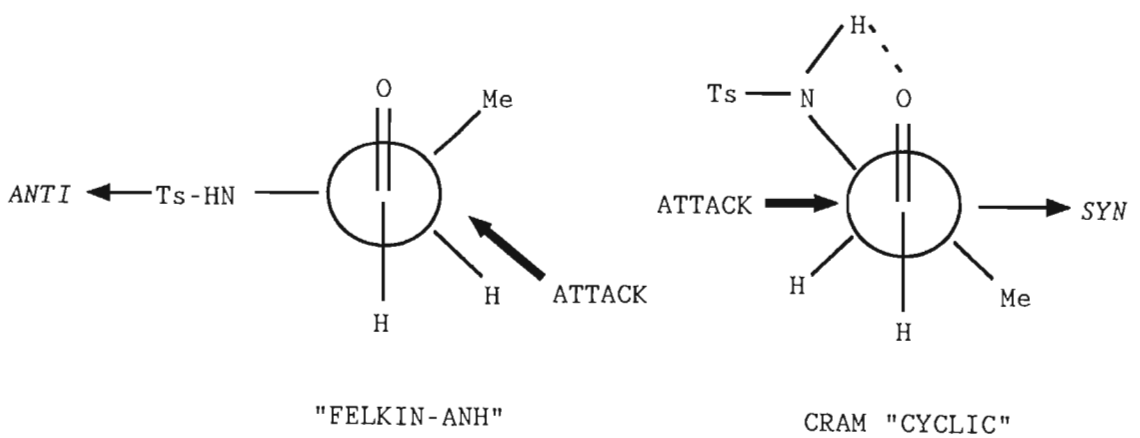


FIGURE 54.

3.1.3.2.3 *N*-PHTHALOYL ALANINAL.

3.1.3.2.3.1. THE METHYL ACRYLATE ADDITION PRODUCT AND DIASTEREOSELECTIVITY.

Analysis of the ^{1}H n.m.r. spectrum of the crude *N*-phthaloyl amino aldehyde (188) reaction mixture revealed the presence of a third, minor component (223), approximately 26% of the crude reaction product in addition to the two diastereomeric products. Subsequent purification of a sample by flash chromatography furnished the analytically pure expected diastereomeric mixture (217), together with a small quantity of the major diastereomer (217 B) which turned out to be a solid.

However, an attempt to isolate this *major* isomer from the remaining crude reaction mixture, by large scale crystallisation, led to isolation of the minor component (223). This compound, fully characterised by n.m.r., GC/MS spectroscopy, elemental analysis and X-ray single crystal structure analysis[184] (FIGURE 55), had the following structure:

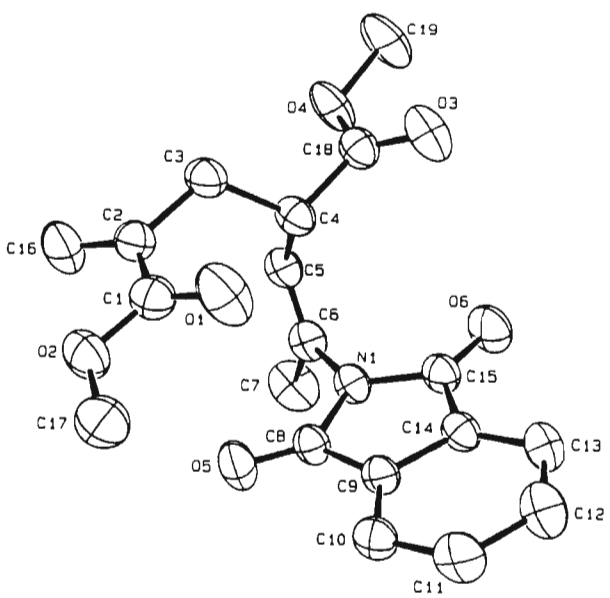
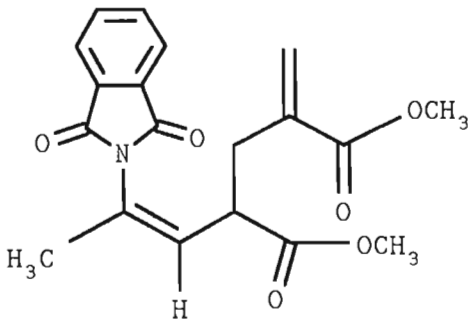


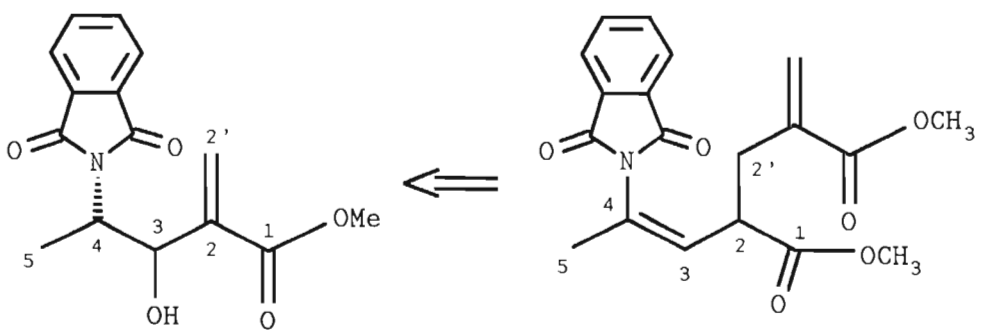
FIGURE 55.



(223)

It was also noted that ^{1}H n.m.r.shift reagent studies on (223) indicated no e.e..

It is evident that this compound is derived from the initially formed coupling product (217) (SCHEME 64).



(217) (223)

SCHEME 64.

Due to the absence of a free *N*H-proton in the *N*,*N*-diprotected amino aldehyde (188), that is, the absence of a

chelated structure in the transition state, one can predict *anti* diastereoselectivity through the "open-chain" Felkin-Anh[30,33] model (FIGURE 56).

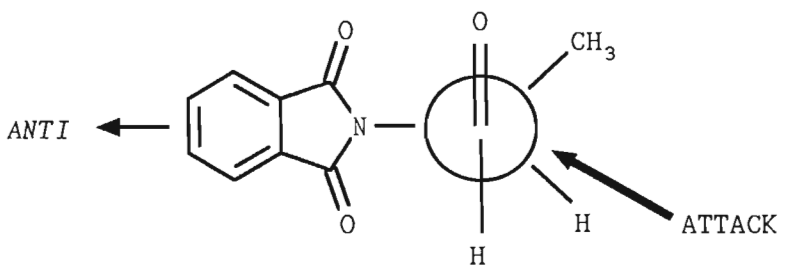
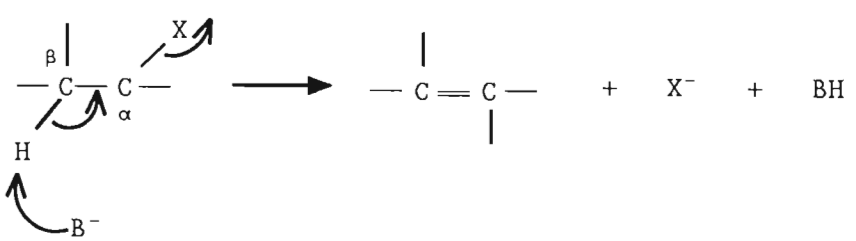


FIGURE 56.

The latter prediction is consistent with observations by Jurczak and Gołębiowski,[48] who noted predominant formation of *syn* adducts, on varying the *N*-protection on alanine-derived *N*-protected amino aldehydes from phthaloyl to Cbz or ^{t}Boc protection, in their diene studies.

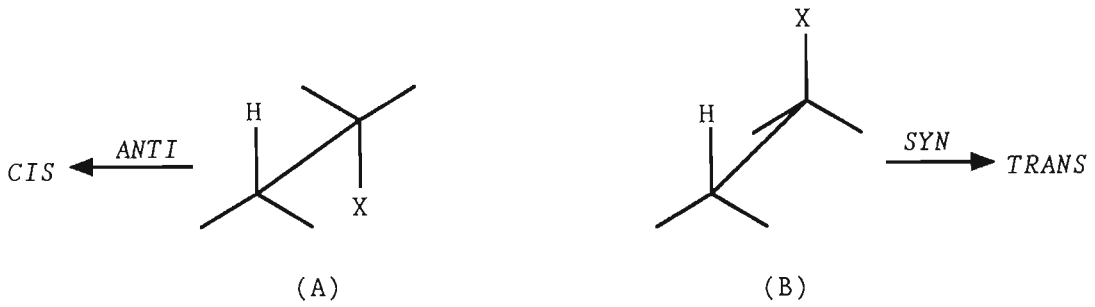
However, the *observed* diastereomeric ratio indicates predominance of the *syn* diastereomer.

The E_2-mechanism/elimination[185] involves simultaneous departure of the two groups, with the proton being abstracted by a base (SCHEME 65).



SCHEME 65.

The mechanism is thus a one step stereospecific one (SCHEME 66).



SCHEME 66.

The five atoms involved in the transition state, including the base, must be in one plane. There are two ways to achieve such a requirement:

(1) H and X may be *trans* to one another (A) with a dihedral angle of 180°. Conformation (A) is *anti*-periplanar, and this type of elimination, in which H and X depart in opposite directions, is referred to as an *anti* elimination.

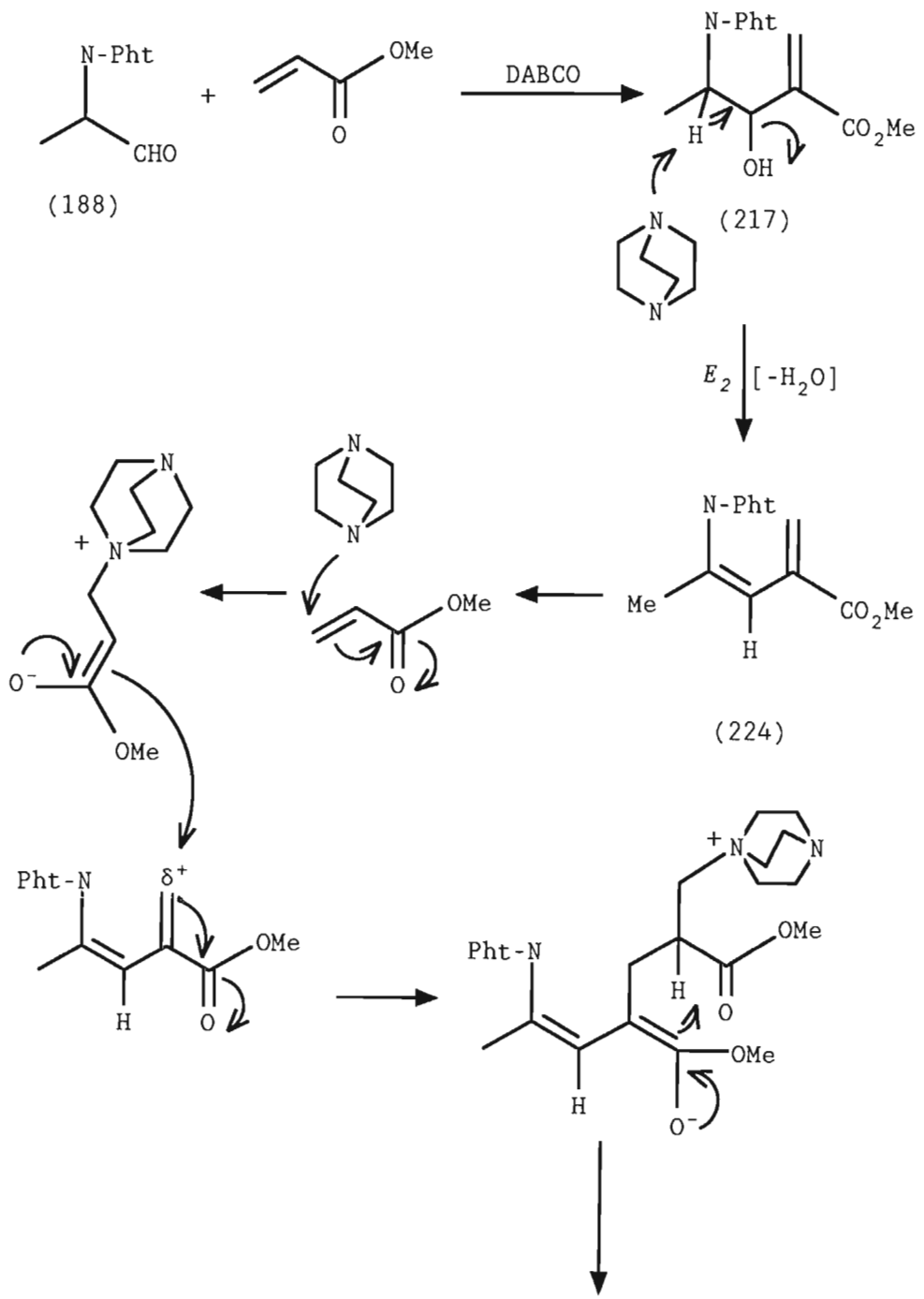
(2) Both H and X may be *cis* to one another (B) with a dihedral angle of 0°. Conformation (B) is *syn*-periplanar, and this type of elimination, with H and X leaving in the same direction, is referred to as a *syn* elimination.

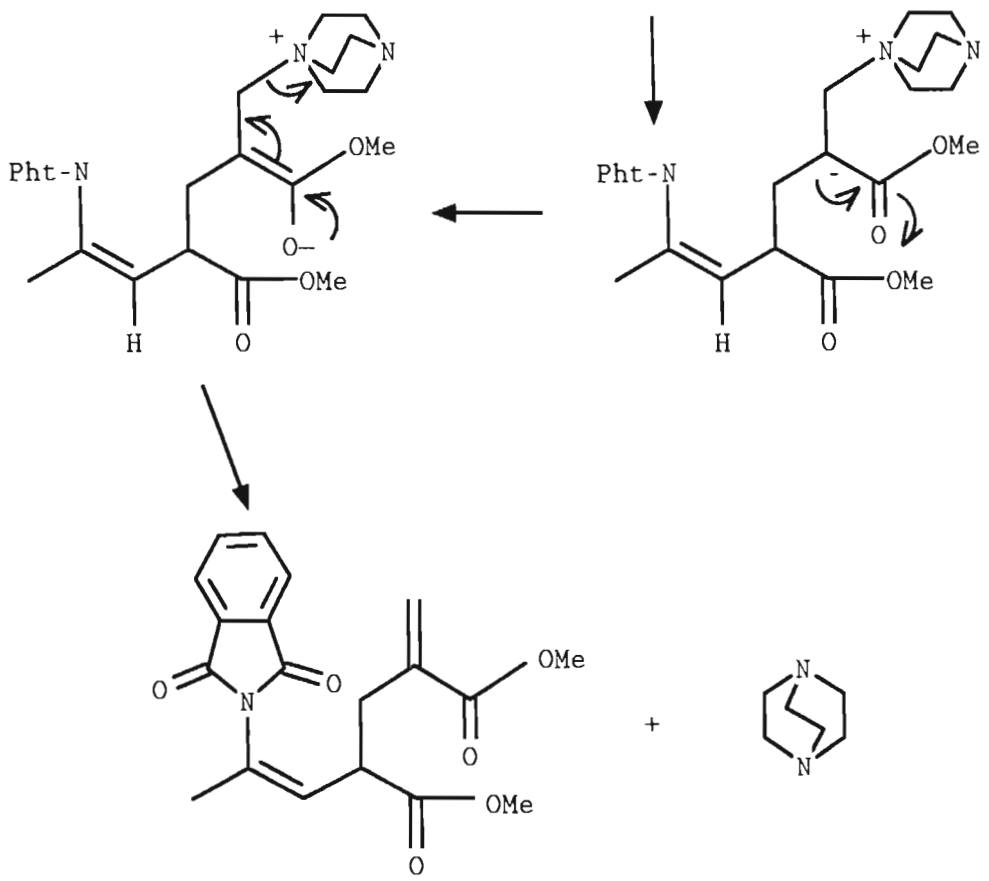
In the absence of special effects, *anti* elimination is usually favoured over *syn* elimination.

When the dihedral angle of 180° required for *anti* elimination cannot be achieved, *anti* elimination is greatly slowed or prevented entirely.

In general, *trans* olefins are formed by *syn* elimination, but *cis* olefins are formed entirely by *anti* elimination.

The following reaction sequence/mechanism has been proposed for formation of the secondary product (223) (SCHEME 67).





(223)

SCHEME 67.

(1) Formation of the classical Baylis-Hillman reaction condensation product (217).
(2) Dehydration of the coupled product (217), by an E_2 reaction, to afford alkene (224).
(3) Subsequent Michael-type addition of a vinyl carbanion to the olefinic moiety of the amino ester (224).
(4) Normal elimination of catalyst to generate the acrylate (223).

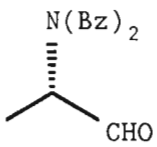
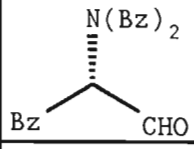
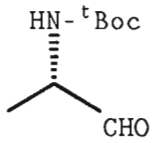
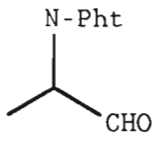
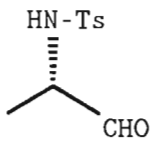
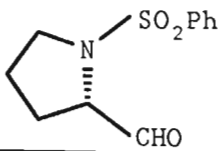
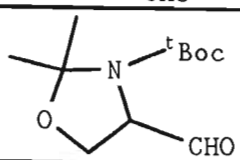
The above finding [*syn* diastereoselectivity for the aldehyde (188)] has two possible implications:

(1) The aldehyde exhibits the predicted *anti* selectivity, but the *anti* diastereomer undergoes preferential E_2 elimination subsequently.
(2) The aldehyde exhibits *syn* selectivity and both diastereomers undergo the E_2 elimination.

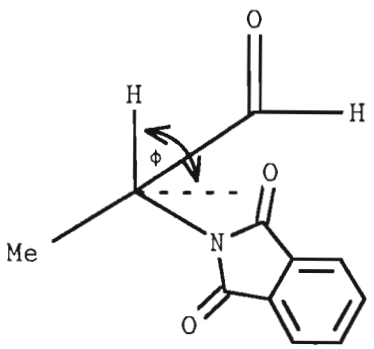
For the diastereomers (217 A/B), Dreiding models suggest that for an *anti* elimination to occur, very little steric discrimination exists between the two diastereomers.

With respect to (2) above, TABLE 26 shows ^{1}H n.m.r. data of the aldehydic proton for the *N*-protected α-amino aldehydes that were utilised in the present study.

TABLE 26: Proton chemical shifts (200 MHz; $CDCl_3$/TMS) for the aldehyde peak in the amino aldehydes.

COMPOUND	ALDEHYDE	δ_{CHO}(ppm)	MULTIPLICITY	COUPLING CONSTANT *J*(Hz)
186		9.71	s	-
187		9.71	s	-
179a		9.57	s	-
188		9.70	s	-
212		9.45	d	1.5
204		9.68	d	2.4
175		9.56	d	2.4

The aldehyde (188) shows a sharp singlet at 9.70 ppm suggesting the conformation below (FIGURE 57) in which the dihedral angle between the aldehydic proton and the one on the α-carbon would be approximately 90°. As a result, it shows a minimum spin-spin coupling.



ϕ = dihedral angle

(197)

FIGURE 57.

One proposal that involves preferential attack of this conformation by the dipolar DABCO-acrylate enolate species (70), from the least hindered topside (FIGURE 58) would give predominantly the *syn* isomer.

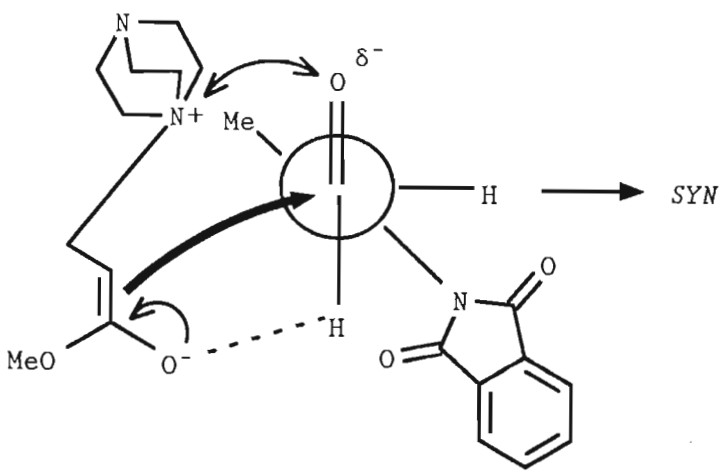


FIGURE 58.

Thus, by extension of Cram's "cyclic" model[26] (for the assumption that: coordination of the cationic fragment of the nucleophile with the carbonyl oxygen - an "electrostatic association"), together with stabilisation of the enolate anion by the hydrogen through an hypothetical eight-membered transition state (FIGURE 58), *syn* selectivity can be rationalised.

The proposed conformation adopted by aldehyde (188) parallels the observation that *syn* selectivity predominated in the organoaluminium additions[186] to the chiral *N*-phthaloyl-protected serine-derived α-amino aldehyde (225) (FIGURE 59).

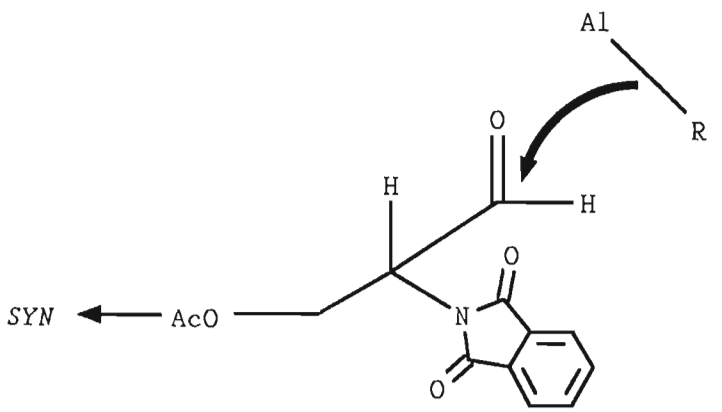


FIGURE 59.

Although *syn* selectivity appears to dominate, *anti* selectivity can also be rationalised by the alternative proposed hydrogen-bonded conformation, as depicted in FIGURE 60.

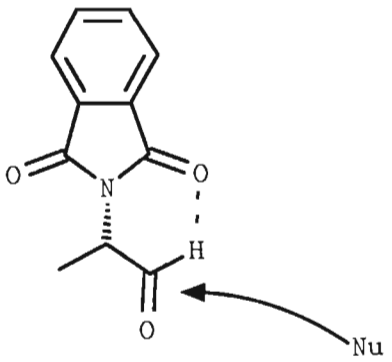
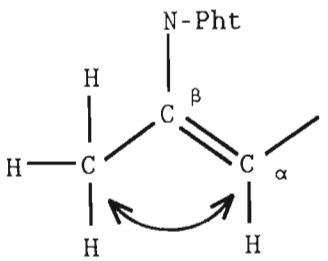


FIGURE 60.

Inspection of the ^{1}H n.m.r. spectrum of the crude reaction mixture revealed the presence of *two* doublets, at 2.03 (*J* 1.34 Hz) and 2.15 (*J* 1.47 Hz), ppm in a virtually 1:1 ratio. This resonance is assigned to the C-5 methyl group of (223), which couples with the α-proton, as shown below.



J = 1.10 Hz

(223)

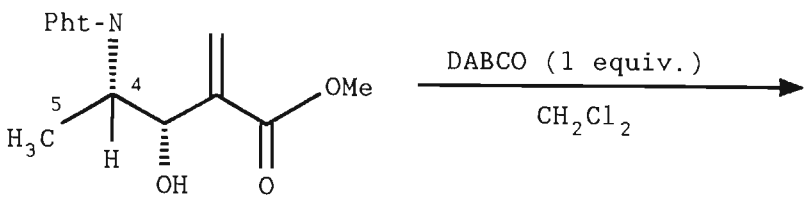
Comparison of the ^{1}H n.m.r. spectra of the isolated isomer [(223) (*Z*, *Z*)] with that of the crude reaction mixture indicated that the *minor* geometric isomer, with its upfield C-5 methyl group chemical shift at 2.03 ppm, had been isolated by the crystallisation procedure. However, its observed coupling constant (*J* 1.10 Hz) was slightly lower.

The fact that the observed coupling constant ^{4}J for the isolated isomer (241) is smaller than its corresponding geometric isomer, suggests a *cis* arrangement of the C-5 methyl group and the α-proton, in accordance with the generalisation that for vicinal protons $J_{cis} < J_{trans}$. This *Z*-configuration of the double bond was unambiguously established by the X-ray crystal structure determination,[184] (FIGURE 55).

Since both the (*Z*) and (*E*) isomers were formed in virtually equal amounts, it is reasonable to propose that both the *anti* and *syn* diastereomers (217 A/B), undergo both modes of elimination, but obviously the relative degree within each cannot be stated or approximated with certainty.

3.1.3.2.3.2 REVERSIBILITY.

In order to provide additional evidence in favour of the proposed mechanism and/or the proposal that the *anti* diastereomer (217 A) undergoes preferential elimination to form the by-product (223), *via* the intermediate (224), the following reaction was carried out (EQUATION 48).



(217 B)

+

diastereomer

(217 A)

EQUATION 48.

The above reaction mixture, enriched in the *syn* isomer (217 B) (54:46), was monitored for the disappearance of the C-5 methyl doublets (*syn* - 1.44 ppm and *anti* - 1.52 ppm) diastereomers. However, it was interesting to note the following:

(1) The *upfield* (*syn*) doublet was decreasing in intensity much faster than the *downfield* (*anti*) doublet.
(2) After 4 days, only *one* doublet (1.49 ppm) was present.
(3) After 8 days, only *one* doublet (1.41 ppm) was present. Other characteristic resonances for the *syn* and *anti* diastereomers were not detectable.
(4) Normal workup of the reaction mixture revealed the presence of *two* doublets (1.44 and 1.52 ppm) in the ^{1}H n.m.r. spectrum. All other resonances for the *syn* and *anti* isomers were detectable.

Subsequent chromatography of the crude product afforded:

(1) A minor fraction containing two components - mostly the *syn* isomer and very little of an unknown component, presumably (224).
(2) A major fraction containing both the *anti/syn* diastereomers (217 A/B).

The above assignments were made by inspection of the n.m.r. spectra as well as GC/MS of the fractions.

For the minor fraction (1), the following n.m.r. data were observable for the unknown component:

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm (proposed assignments, where possible, in parenthesis):

2.15 (d, *J* 1.5 Hz, CH_3-C=CH)
3.43 (d, *J* 8.1 Hz,)
3.73 (s, CO_2-CH_3)
3.78 (s, CO_2-CH_3)

5.25 (m, CH_3-C*H*=CH)
5.40 (d, *J* 1.0 Hz, vinyl C*H*=C)
6.11 (d, *J* 0.9 Hz, vinyl C*H*=C)

^{13}C n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

18.85 (q, CH_3)
28.89 (t, CH_2)
44.05 (d, *C*H)
52.10 (q, CO_2CH_3)
52.13 (q, CO_2CH_3)
123.27 (d, *C*H=*C*H aromatics)
125.36 (t, CH_2=C)
131.04 (s, -*C*=*C*- aromatics)
131.85 (s, -*C*=*C*- aromatics)
134.06 (d, *C*H=*C*H)
134.29 (s, N*C*=CH)
141.16 (s, *C*=CH_2)
167.30 (s, *C*OOMe/N*C*O)
167.61 (s, *C*OOMe/N*C*O)

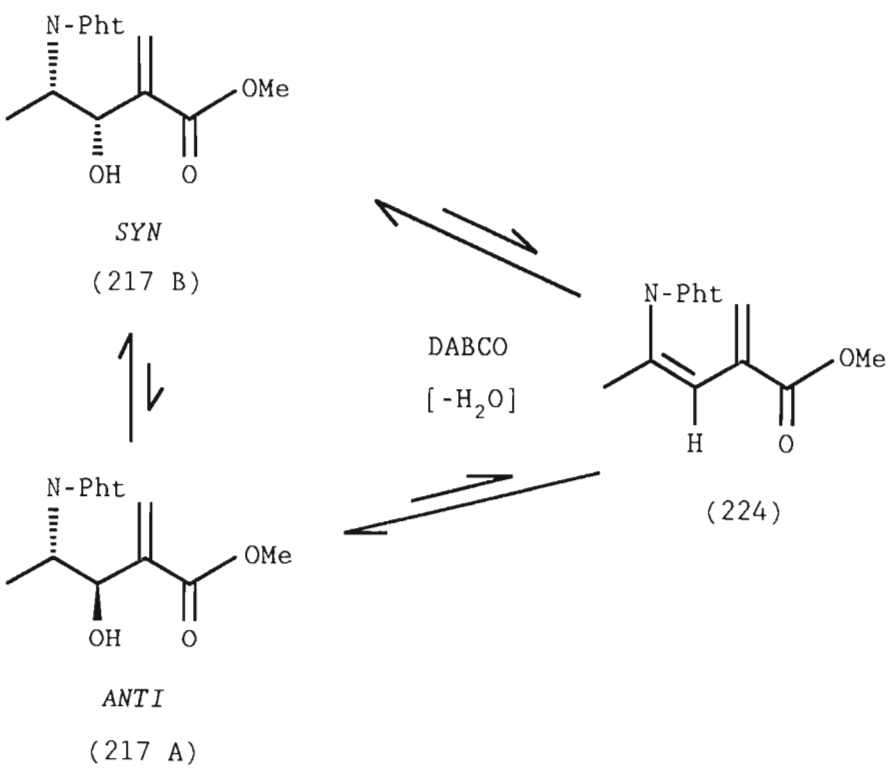
The mass spectral data [molecular weight = 271.28 for the intermediate (224)] are as follows:

m/z (EI):

271(*M*$^+$, 0.13), 256(0.07), 240(0.75), 212(1.77), 186(0.50), 174(100), 173(0.53), 146(3.19), 113(0.13), 94(0.08), 85(0.22), 77(5.94), 76(11.47), 75(2.51), 70(0.88), 59(0.72), 54(1.02) and 44(0.19).

In view of the above-mentioned findings, we propose the following:

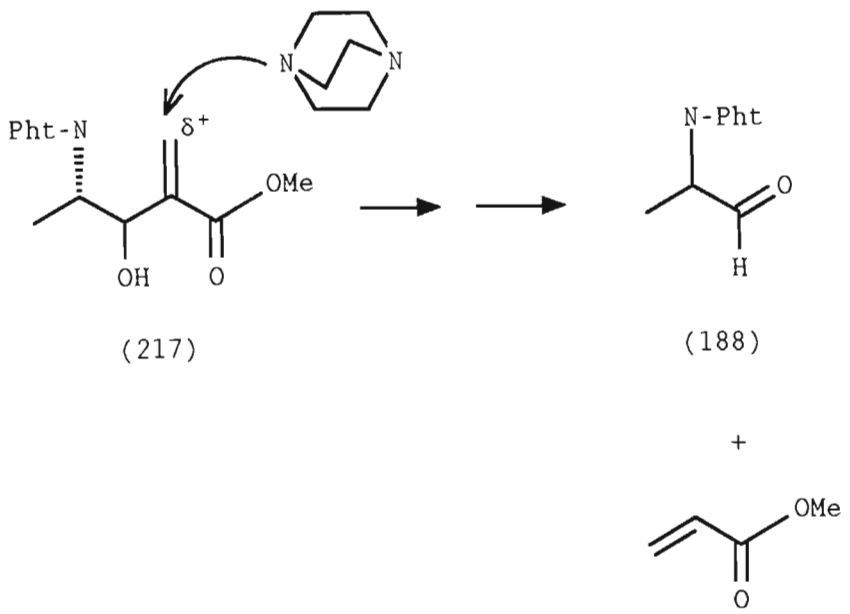
(1) The proposed β-hydrogen elimination is operative due to the disappearance of any one of the methyl doublets during the reaction.
(2) The *syn* diastereomer undergoes the proposed E_2 elimination much faster than the *anti* isomer.
(3) Possible *anti/syn* equilibration, where the *syn* isomer, in this instance, appears to be the more stable diastereomer, in addition to the *reversibility* of the Baylis-Hillman reaction (SCHEME 68).



SCHEME 68.

The latter proposal supports earlier speculations (SCHEME 27) (CHAPTER 2) concerning the general reversibility of the Baylis-Hillman reaction.

Alternatively, addition of catalyst (amine) to the vinyl system to generate the starting materials, is also feasible (SCHEME 28) (CHAPTER 2).



SCHEME 28.

However, in this instance, the corresponding aldehyde peak (9.70 ppm) was not detectable at any stage of the "test" reaction.

(4) Addition of the acrylate anion to the intermediate (224), leading to the formation of (223), is not favoured except when excess methyl acrylate is present.

In view of the fact that a relatively larger amount of substrate [aldehyde (197): 43 mmol], was used in addition to the presence of an excess of vinyl "carbanion" (methyl acrylate) and one equivalent of catalyst, formation of the compound (223), and hence its detection and isolation seems feasible. The much lower yield of the desired diastereomeric

product (217) can possibly be attributed, in part, to this side reaction.

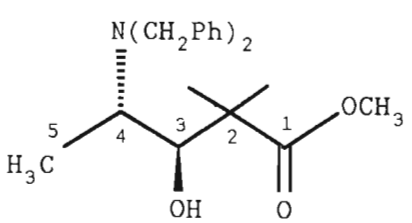
Dimerisation of β-unsubstituted, α,β-unsaturated compounds have been catalysed by transition metal catalysts[187] and trialkyl phosphine.[188] In addition, DABCO-catalysed[73,142,189] dimerisations have also been reported.

3.1.3.2.4 ASSIGNMENT OF STEREOSUBSTRUCTURE (RELATIVE CONFIGURATION).

The relative stereochemical assignments of the β-hydroxy -γ-amino esters were made utilising the previously described methods for the α-alkoxy aldehyde-coupled adducts. In addition to these methods, assignments were also made on the basis of n.m.r studies and X-ray structure determination. These will be reviewed below.

3.1.3.2.4.1 USE OF N.M.R. DATA (METHOD H).

The following data, indicated below the respective compounds, were accessible[174] on the γ-amino aldol adducts.



anti

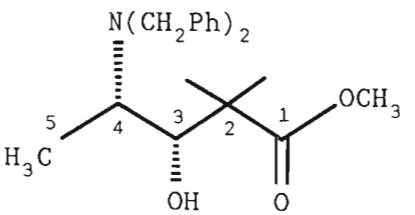
(225a)

^{1}H n.m.r. (400 MHz; $CDCl_3$/TMS) δ/ppm:

1.04 (3 H, d, *J* 6.8 Hz, H-5)
2.89 (1 H, m, H-4)
3.61 (3 H, s, COO-C*H*$_3$)
3.92 (1 H, m, H-3)

^{13}C n.m.r. (100 MHz; $CDCl_3$/TMS) δ/ppm:

8.97 (q, C-5)
52.66 (d, C-4)
54.11 (t, N-*C*H$_2$)
78.97 (d, C-3)
177.99 (s, C-1)



syn

(225b)

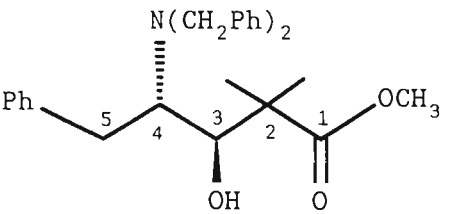
^{1}H n.m.r. (400 MHz;$CDCl_3$/TMS) δ/ppm:

0.95 (3 H, d, *J* 6.7 Hz, H-5)
2.76 (1 H, m, H-4)
3.60 (3 H, s, COO-C*H*$_3$)
3.77 (1 H, d, *J* 9.2 Hz, H-3)

^{13}C n.m.r. (100 MHz; $CDCl_3$/TMS) δ/ppm:

9.03 (q, C-5)
53.24 (d, C-4)
54.51 (t, N-CH_2)
74.70 (d, C-3)
177.68 (s, C-1)

The above proton n.m.r. data indicate a *downfield* shift of H-3 and the methoxy group, for the *anti* isomer. With respect to the carbon chemical shifts, it is evident that C-5 and the benzylic (NCH_2) carbons are shifted *upfield* for the *anti* isomer.



anti

(226a)

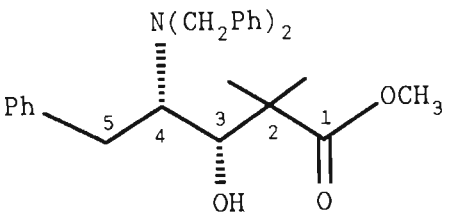
^{1}H n.m.r. (300 MHz; $CDCl_3$/TMS) δ/ppm:

3.67 (3 H, s, OCH_3)
4.13 (1 H, d, H-3)

^{13}C n.m.r. (75 MHz; $CDCl_3$/TMS) δ/ppm:

32.84 (t, C-5)
53.65 (t, N-CH_2)
59.08 (d, C-4)

59.08 (d, C-4)
74.99 (d, C-3)
178.05 (s, C-1)



syn

(226b)

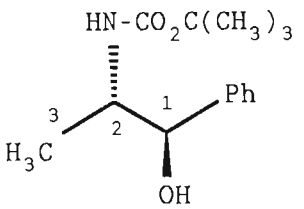
^{1}H n.m.r. (300 MHz; $CDCl_3$/TMS) δ/ppm:

3.65 (3 H, s, O-CH_3)
3.75 (1 H, d, H-3)

^{13}C n.m.r. (75 MHz; $CDCl_3$/TMS) δ/ppm:

34.78 (t, C-5)
53.95 (t, N-CH_2)
59.63 (d, C-4)
73.76 (d, C-3)
177.856 (s, C-1)

The proton n.m.r. data indicate a *downfield* shift for H-3 and the methoxy group for the *anti* isomer. The carbon shifts indicate an *upfield* shift for C-4 and C-5, while C-1 and C-3 are shifted *downfield* for the *anti* isomer.



anti

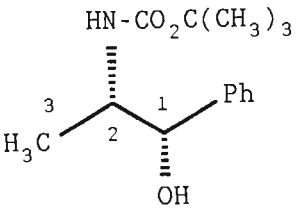
(227a)

^{1}H n.m.r. (400 MHz; $CDCl_3$/TMS) δ/ppm:

0.97 (3 H, d, *J* 6.8 Hz, H-3)
1.45 (9 H, s, $C[CH_3]_3$)
3.98 (1 H, m, H-2)
4.69 (1 H, m, H-1)

^{13}C n.m.r. (100 MHz; $CDCl_3$/TMS) δ/ppm

14.56 (q, C-3)
28.25 (q, $C[CH_3]_3$)
51.87 (d, C-2)
76.46 (d, C-1)
79.61 (s, $C[CH_3]_3$)
156.19 (s, N-COO)



syn

(227b)

^{1}H n.m.r. (400 MHz; $CDCl_3$/TMS) δ/ppm:

1.07 (3 H, d, *J* 6.8 Hz, H-3)
1.41 (9 H, s, $C[CH_3]_3$)
3.87 (1 H, m, H-2)
4.54 (1 H, m, H-1)

^{13}C n.m.r. (100 MHz; $CDCl_3$/TMS) δ/ppm:

17.60 (q, C-3)
28.33 (q, $C[CH_3]_3$)
52.40 (d, C-2)
77.94 (d, C-1)
79.66 (s, $C[CH_3]_3$){
156.36 (s, N-COO)

The proton n.m.r. data indicate a *downfield* shift for the methyl group (H-3) and an *upfield* shift for the *tert*-butyl resonances for the *syn* diastereomer. The carbon chemical shifts indicate a *downfield* shift for the carbinol (C-1) and methyl (C-3) carbons for the *syn* isomer.

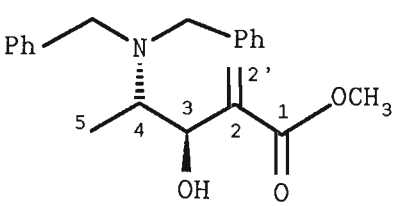
3.1.3.2.4.2 USE OF X-RAY CRYSTALLOGRAPHY (METHOD I).

X-ray crystal structure determination[190] is a useful diagnostic tool for the assignment of stereosubstructure and is therefore most often used as an additional confirmation method.

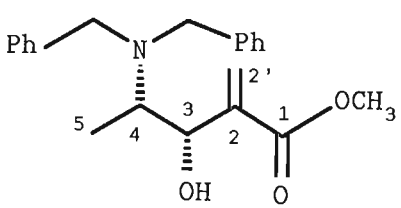
3.1.3.2.4.3. UTILISATION OF THE DESCRIBED METHODS.

Thus, methods (A-I) utilised for the assignment of stereosubstructure, will be indicated below the respective compounds.

COMPOUND 193



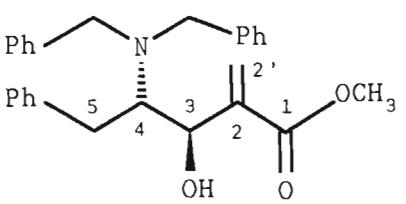
ANTI (MAJOR)
(193 A)



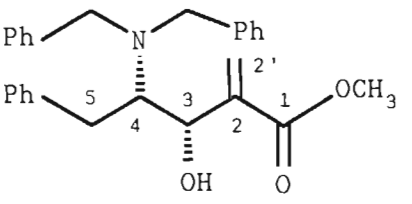
SYN (MINOR)
(193 B)

Methods A, B, C, G and H.

COMPOUND 216



ANTI (MAJOR)
(216 A)



SYN (MINOR)
(216 B)

Methods B, G, H, and I.

FIGURE 58 shows the X-ray structure[191] of (216 A).

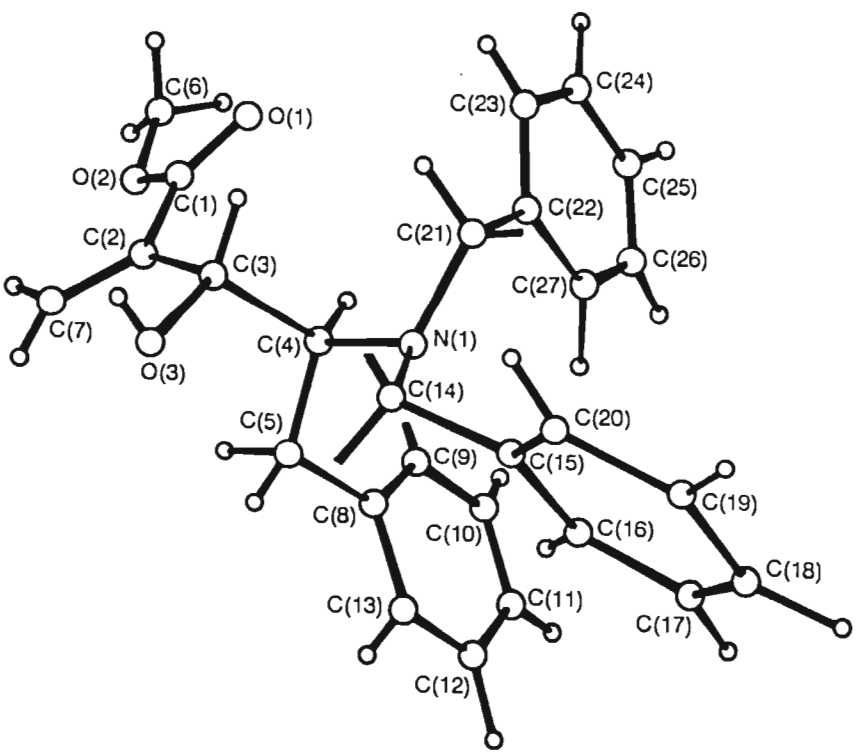
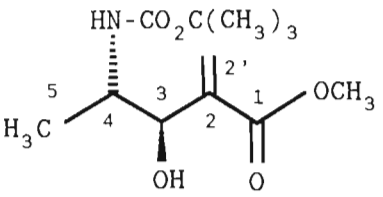
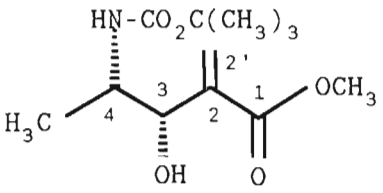


FIGURE 58.

COMPOUND 196



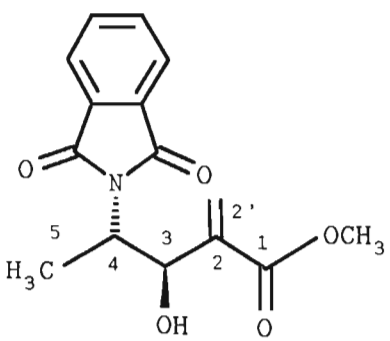
ANTI (MINOR)
(196 A)



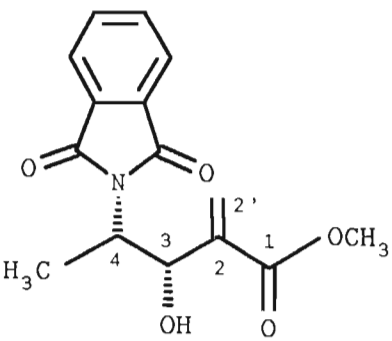
SYN (MAJOR)
(196 B)

Methods B, C, G and H.

COMPOUND 217



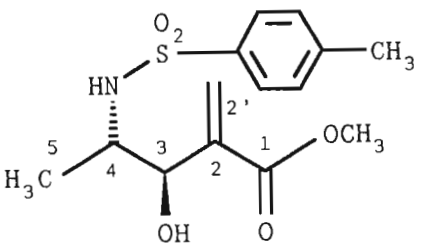
ANTI (MINOR)
(217 A)



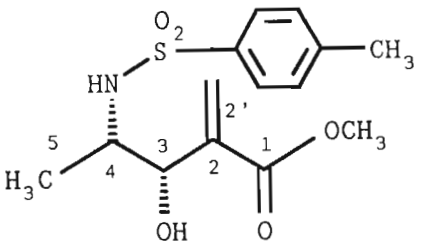
SYN (MAJOR)
(217 B)

Method G.

COMPOUND 218



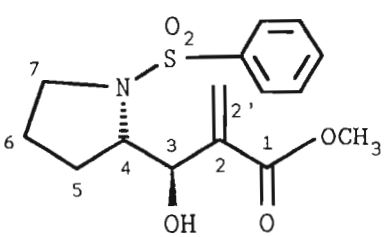
ANTI (MINOR)
(218 A)



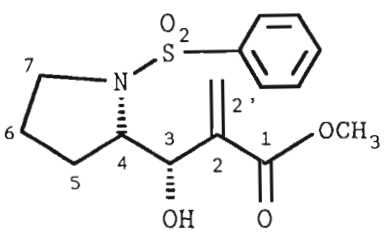
SYN (MAJOR)
(218 B)

Methods B, C and G.

COMPOUND 219



ANTI (MAJOR)
(219 A)



SYN (MINOR)
(219 B)

Method G and I.

FIGURE 59 shows the X-ray[192] structure of (219 A).

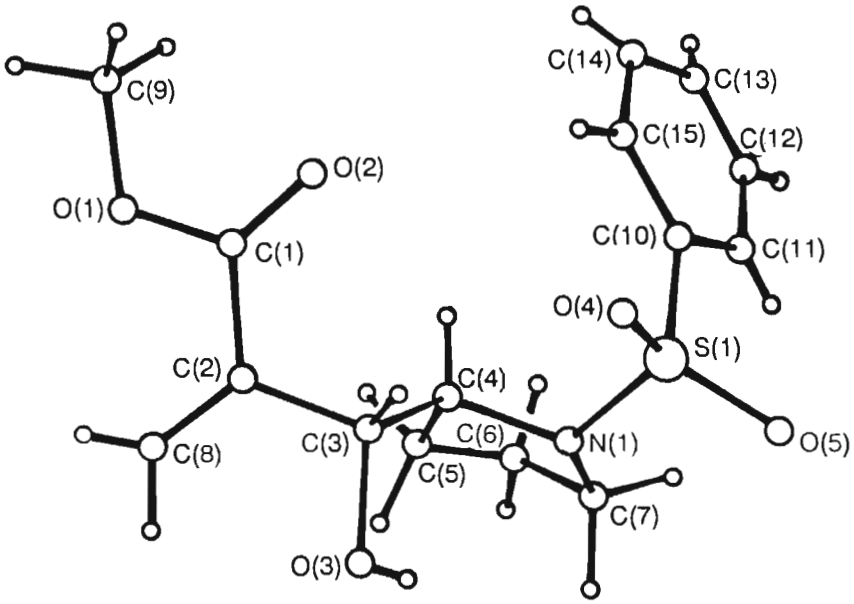
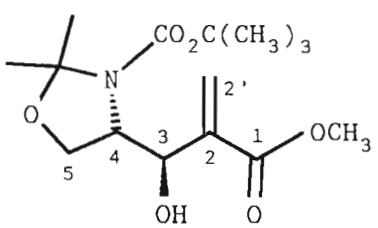


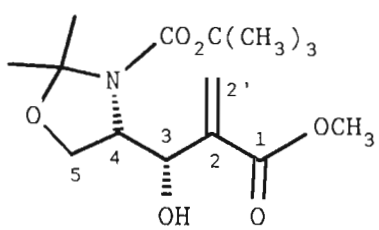
FIGURE 59.

COMPOUND 220.



ANTI (MAJOR)

(220 A)



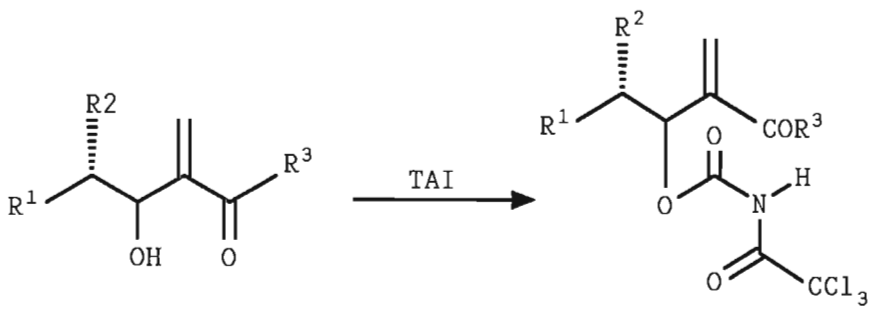
SYN (MINOR)

(220 B)

Method G.

3.1.3.2.4.4 USE OF TAI.

It is obvious that, as with the assignment of stereosubstructure to the alkoxy aldehyde derived products, the above methods are all time consuming, require relatively purified diastereomers/diastereomer mixtures and achievement of adequate resolution of specific resonances. Thus, TAI-derivatisation was again utilised as a diagnostic tool to confirm the *anti/syn* (relative) configuration of these α-methylene-β-hydroxy-γ-amino esters (EQUATION 40).



(124) $R^3 = OCH_3$ (168)

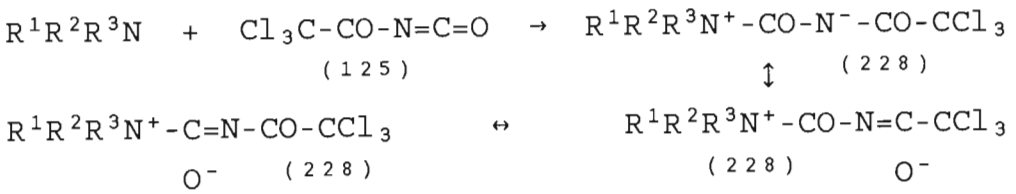
EQUATION 40.

However, since TAI reacts with amines[131] as well (EQUATION 49) forming probable derivatives of the type (228)[131] (SCHEME 69), two equivalents of TAI were consequently utilised for the derivatisation of the tertiary amino aldol adducts (193) and (216).

$R\text{-}NH_2 + Cl_3C\text{-}CO\text{-}N{=}CO \rightarrow R\text{-}NH\text{-}CO\text{-}NH\text{-}CO\text{-}CCl_3$

$R^1R^2\text{-}NH + Cl_3C\text{-}CO\text{-}N{=}CO \rightarrow R^1R^2\text{-}N\text{-}CO\text{-}NH\text{-}CO\text{-}CCl_3$

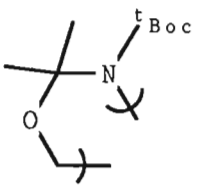
EQUATION 49.



SCHEME 69.

TABLE 27 lists the data obtained.

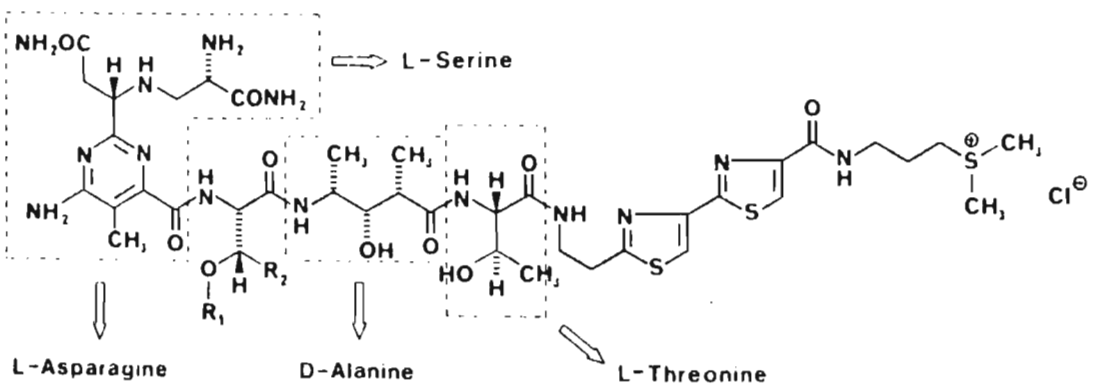
TABLE 27: Carbamate chemical shifts (^{1}H n.m.r.; 200 MHz/$CDCl_3$/TMS) of TAI derivatives (168) of the γ-amino (*anti*/*syn*) diastereomeric mixtures.

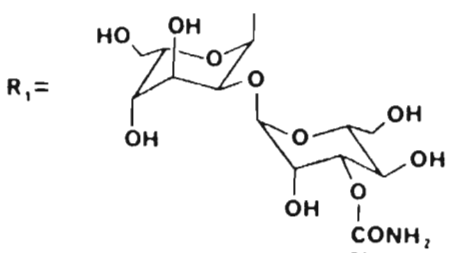
COMPOUND	R^1	R^2	R^3	δ_{NH} (ppm)		$\delta_{SYN}-\delta_{ANTI}$ Δ (ppm)
				SYN	*ANTI*	
193	Me	$N(Bz)_2$	OCH_3	8.523	8.387	+0.136
216	Bz	$N(Bz)_2$	OCH_3	8.494	8.129	+0.365
196	Me	HN-^{t}Boc	OCH_3	8.860	8.815	+0.045
217	Me	N-Pht	OCH_3	8.718	8.627	+0.091
218	Me	HN-Ts	OCH_3	8.938	8.658	+0.280
219	—$(CH_2)_4$-N(Ts)-		OCH_3	8.831	8.672	+0.159
220			OCH_3	8.765	8.666	+0.099

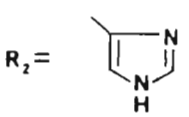
3.1.3.3 ATTEMPTED ELABORATION OF THE DERIVED γ-AMINO ESTERS.

3.1.3.3.1 4-AMINO-3-HYDROXY-2-METHYLPENTANOIC ACID.

Bleomycin[193] (229) is an important antitumour antibiotic which is used clinically in the treatment of squamous cell carcinoma and malignant lymphoma.





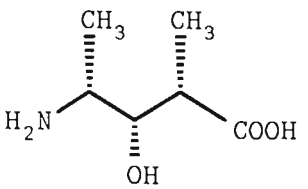


(229)

This highly complex molecule is interesting in that the chirality in several portions of its structure can be derived from various amino acids.

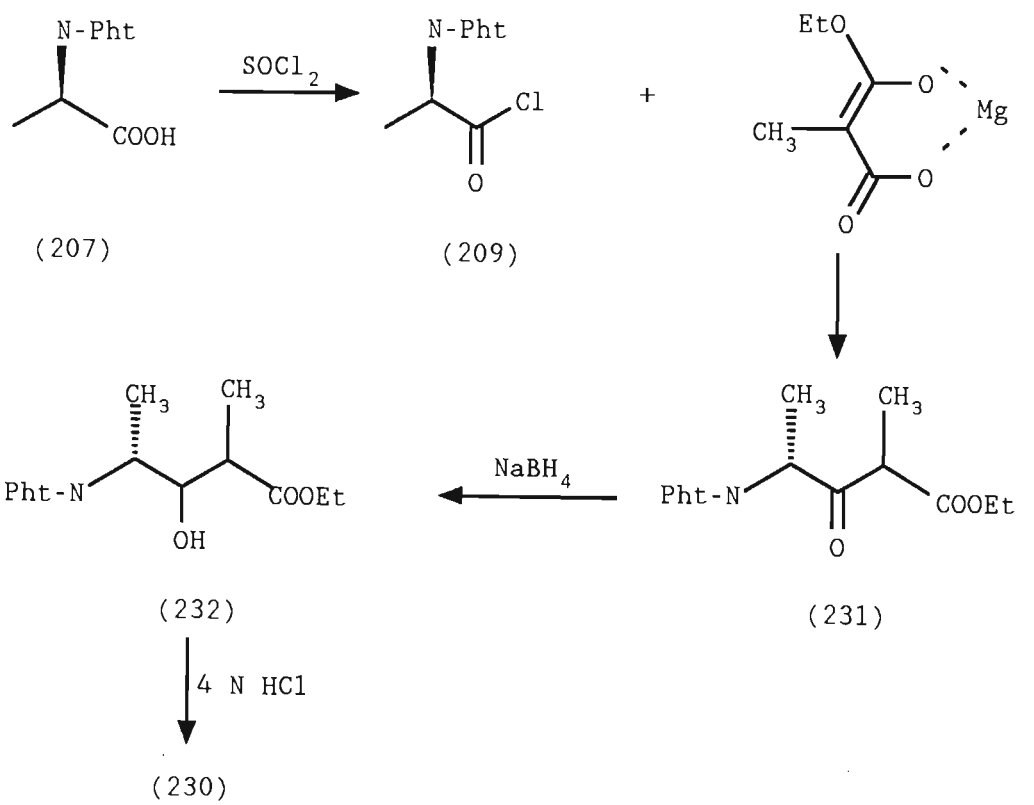
3.1.3.3.1.1 PUBLISHED ROUTES TO THE ACID.

The total synthesis of Bleomycin is accomplished[194] by a series of coupling reactions of seven building blocks, one of them being (2S, 3S, 4R)-4-amino-3-hydroxy-2-methyl-pentanoic acid (230), derivable from (D)-alanine.



(230)

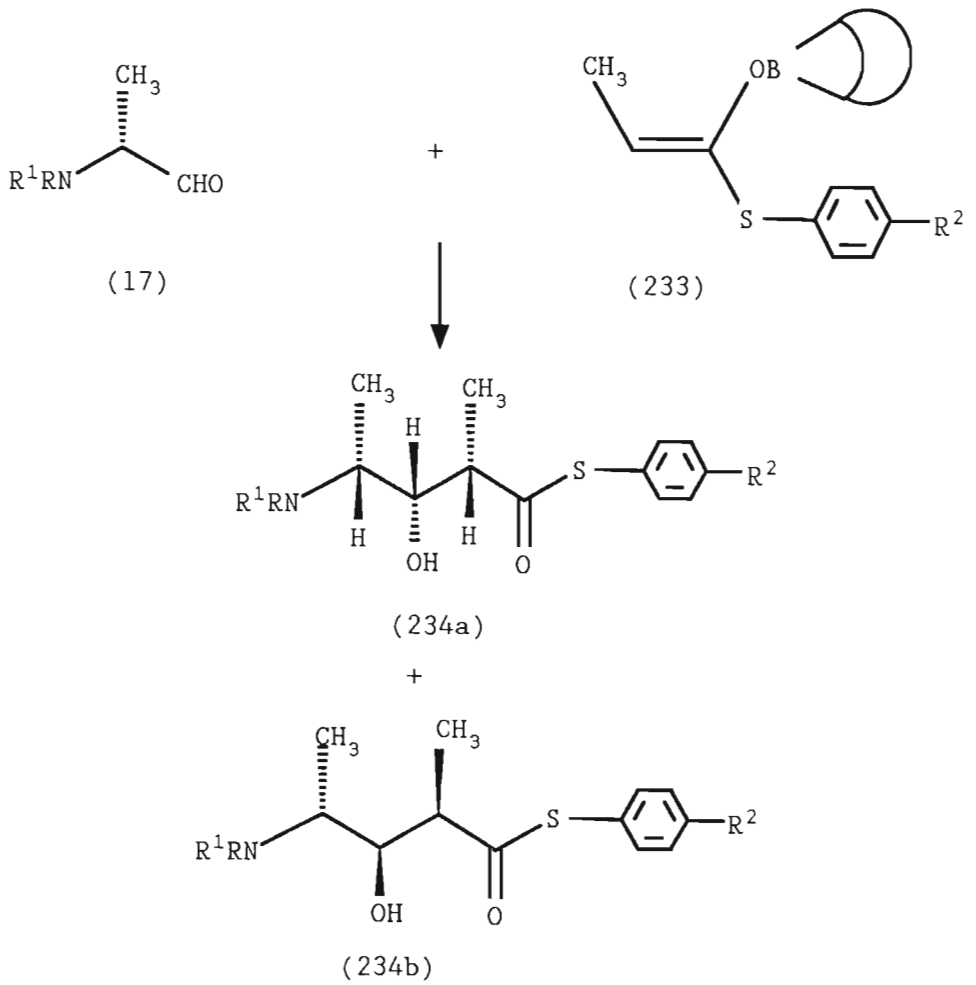
The first reported[195] synthesis of (230) appeared in 1974 (SCHEME 69).



SCHEME 69.

After final hydrolysis, separation afforded (230) in 12.2% yield.

It is obvious that this process is not an efficient one; therefore a more efficient, stereoselective synthesis of (230) is desired in order to increase its overall yield and to alleviate the tedious separation of diastereomers. In 1982, the problem was solved by Ohno and co-workers[176] who reported a facile and stereoselective synthesis of (230) (SCHEME 70).



R = Pht, Cbz, ^{t}Boc

R^1 = Pht, H

R^2 = H, NO_2

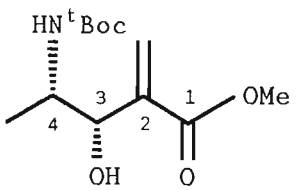
SCHEME 70.

Aldol condensation of variously *N*-protected chiral (R) amino aldehydes (17), obtained from (D)-alanine, were examined under different reaction conditions with (*E*)-vinyloxyborane derivatives (233). The overall yield of the diastereomeric aldol products was generally good. The high *syn* diastereoselectivity of this reaction (234a:234b = 8:1 → 35:1) was rationalised[176] by using the commonly accepted six-membered cyclic transition state.

This procedure enjoys the additional advantage that the products (234a) are activated esters and can be readly employed in the coupling reaction leading to Bleomycin.[196]

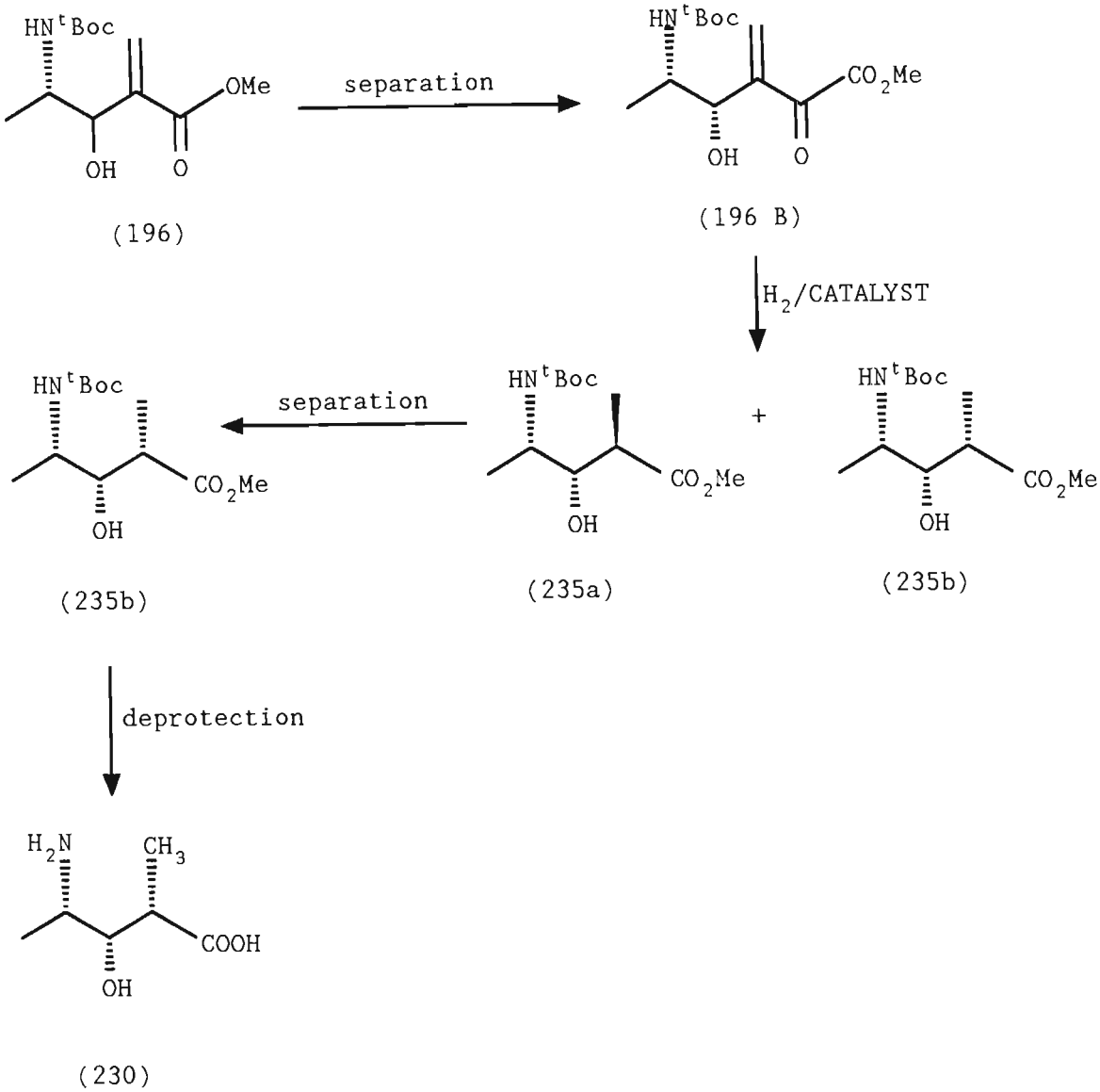
3.1.3.3.1.2 ATTEMPTED USE OF THE *SYN* ADDUCTS.

In our case, an obvious precursor to the amino acid (230) is the major *syn* diastereomer (196 B) with the desired 3,4-*syn* configuration.



(196 B)

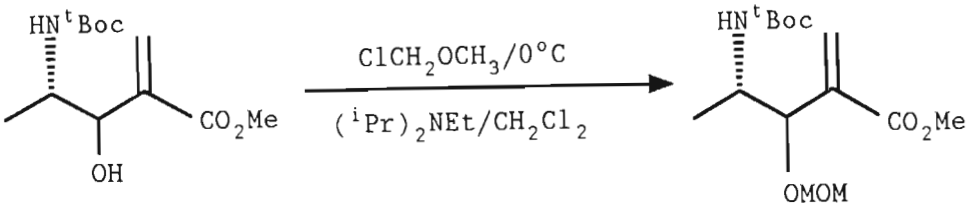
A possible route to the acid (230) is outlined in SCHEME 71.



SCHEME 71.

However, chromatographic separation of the diastereomers of (196) turned out to be a stumbling block.

An alternative would be to derivatise any one functionality present in (196). Thus, the alcohol group was initially protected as the MOM ether by standard procedure[68] (EQUATION 50).

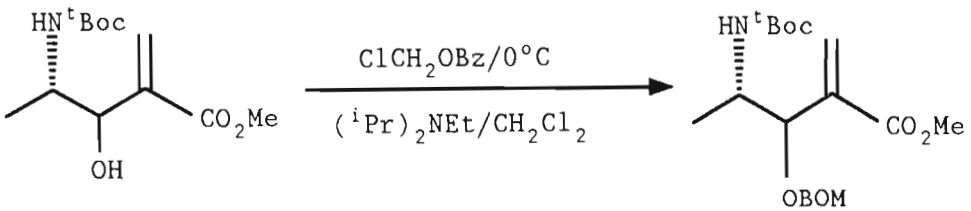


(196) (236)

EQUATION 50.

Unfortunately, this derivatised mixture (236) again could not be separated.

The BOM-protecting group was then used, because of its "UV tag" by virtue of the presence of the phenyl moiety (EQUATION 51).

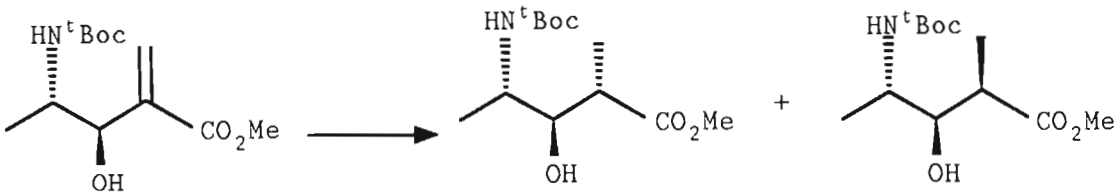


(196) (237)

EQUATION 51.

Although the hydroxyl group protection proceeded under the standard conditions,[68] the corresponding product (237), though UV-active, was a single spot on t.l.c. and the diastereomers were again inseparable by flash chromatography.

An alternative route was envisaged via direct hydrogenation of the diastereomeric mixture (196). However, due to the observation that hydrogenation[70] of β-hydroxyalkyl acrylates proceeds with *anti* selectivity, the tedious separation of the four possible diastereomers would exist (SCHEME 71), i.e., (253a/b) in addition to the two possible products from the minor *anti* diastereomer (196 A) (EQUATION 52).



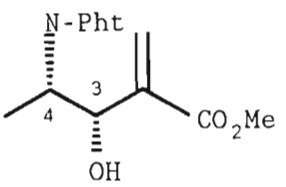
(196 A) (235c) (235d)

EQUATION 52.

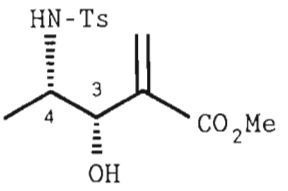
Even if separation and isolation of (196 B) is possible, this would ultimately lead to the other enantiomer of (230) in racemic form, in view of the fact that:

(1) The starting aldehyde (179a), being derived from (L)-alanine, had the opposite configuration.
(2) The observed rotation on the diastereomeric mixture (196) was zero, possibly due to racemisation of the aldehyde.

Other possible substrates that can be used in the projected synthesis (SCHEME 71) include the diastereomeric mixtures (217) and (218) (FIGURE 60), which are enriched with the required 3,4-*syn* diastereomer. However, (217) could not be separated into the two diastereomers. Furthermore, in this derived system (217), the starting aldehyde (188) was prepared in racemic form, so that the acid (230) would again be obtained as a racemate.



(217 B)

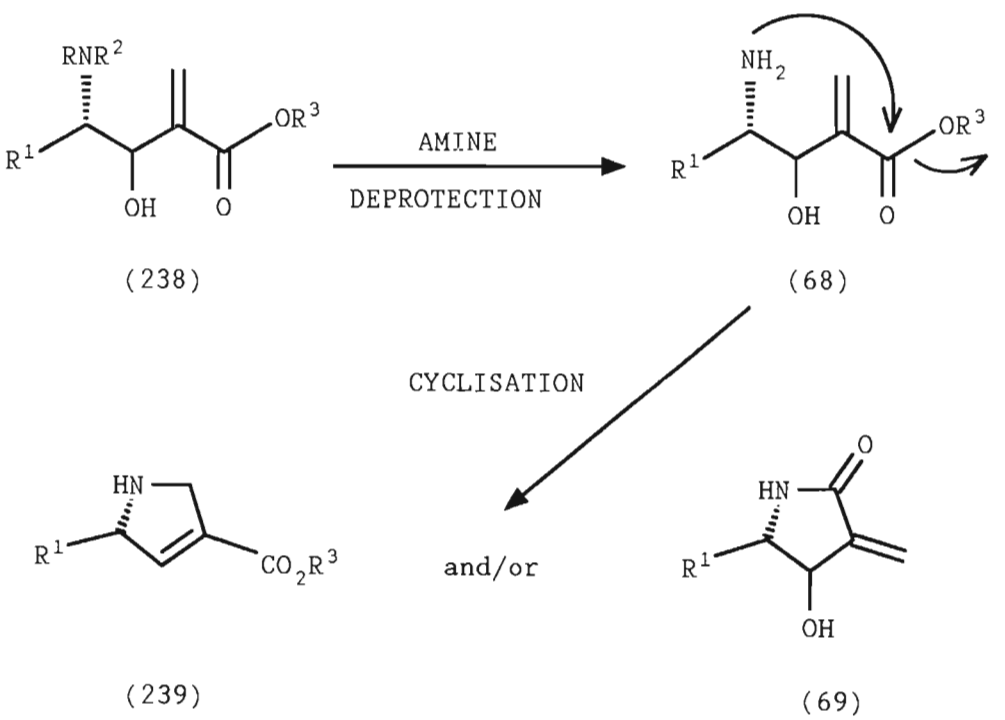


(218 B)

FIGURE 60.

3.1.3.3.2 THE α-METHYLENE-γ-LACTAMS.

Compounds of the type (238) also offer a possible route to the α-methylene-β-hydroxy-γ-lactams (69), as stated in the introduction (SCHEME 13) (CHAPTER 1).



(238)

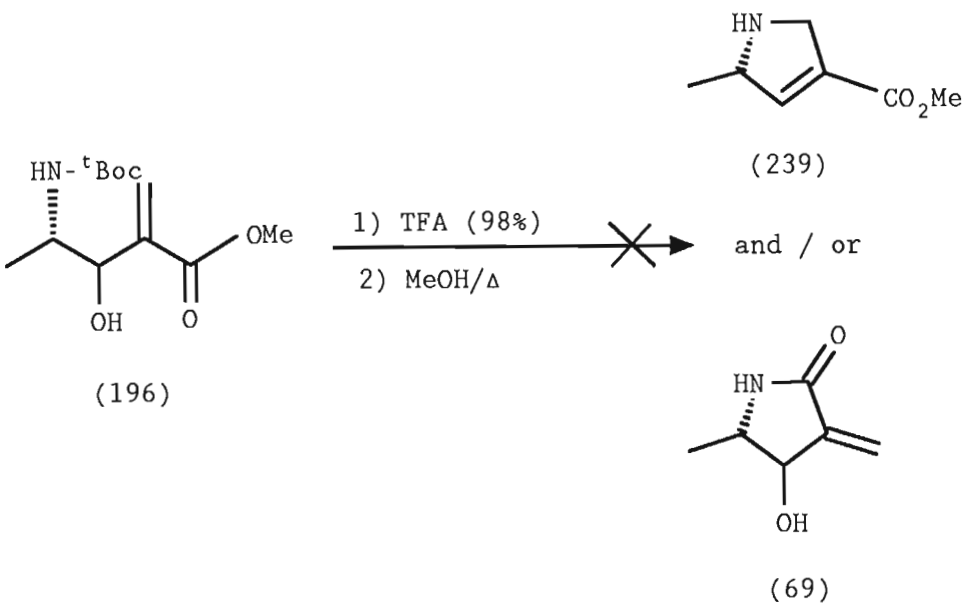
(68)

(239)

(69)

SCHEME 13.

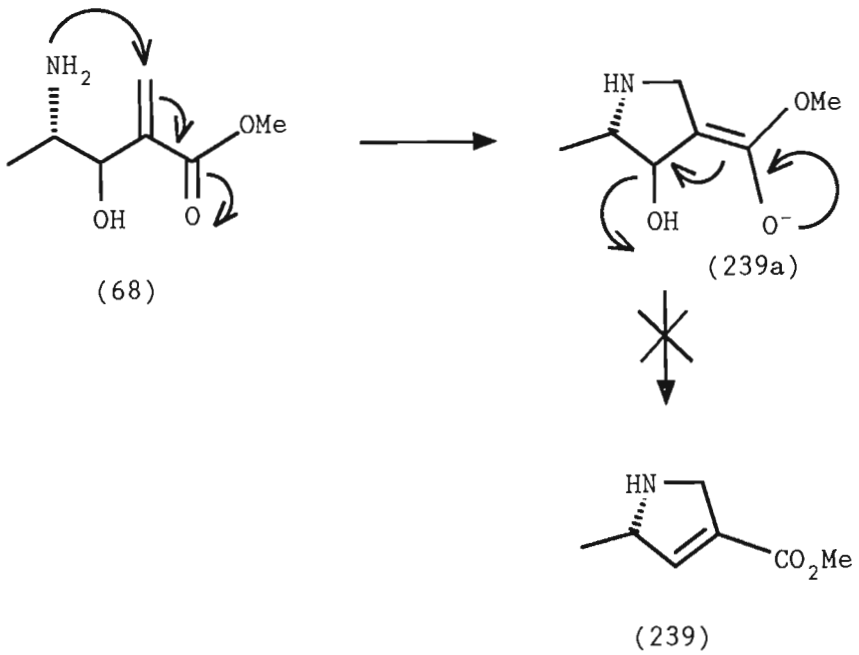
However, trifluoroacetic acid-deprotection of (196), followed by refluxing the intermediate (crude) deprotected amino alcohol (which was *not isolated*) in methanol, was not successful (EQUATION 53).



EQUATION 53.

The target molecule (69), or any significant material, could not be isolated from the complex reaction mixture after purification by flash chromatography.

The observation that even the other possible cyclisation product (239) could not be isolated could not be rationalised.



SCHEME 72.

Bode and Kaye,[197] however, observed that replacement of the hydroxy function by a better leaving group (OAc) facilitated the elimination step, in their route to indolozines.

However, this investigation was not carried further.

3.1.4 RACEMISATION OF THE AMINO ALDEHYDES.

It should be noted that the aldehydes [(186), (187), (179a) and (204)] were prepared and subsequently reacted in optically pure form. However, optical rotations determined on the corresponding diastereomeric mixtures and the separated diastereomers [(193), (216), (196) and (219)] respectively, showed them to be optically inactive, implying that these aldehydes had racemised under the basic

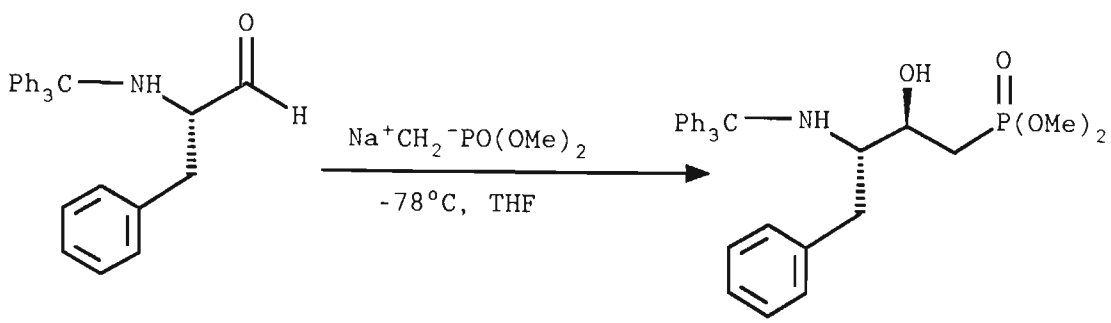
(amine-catalysed) reaction conditions.

3.1.4.1 ACID-CATALYSED RACEMISATION.

Racemisation of Cbz-*N*-protected amino aldehydes under acidic conditions, e.g., on exposure to silica gel, has been reported[161] (SCHEME 40) (CHAPTER 3). We have also observed that the latter occurs during the purification step by flash chromatography, by a similar mechanism as proposed for the analogous alkoxy aldehydes (SCHEME 38) (CHAPTER 2).

3.1.4.2 BASE-CATALYSED RACEMISATION.

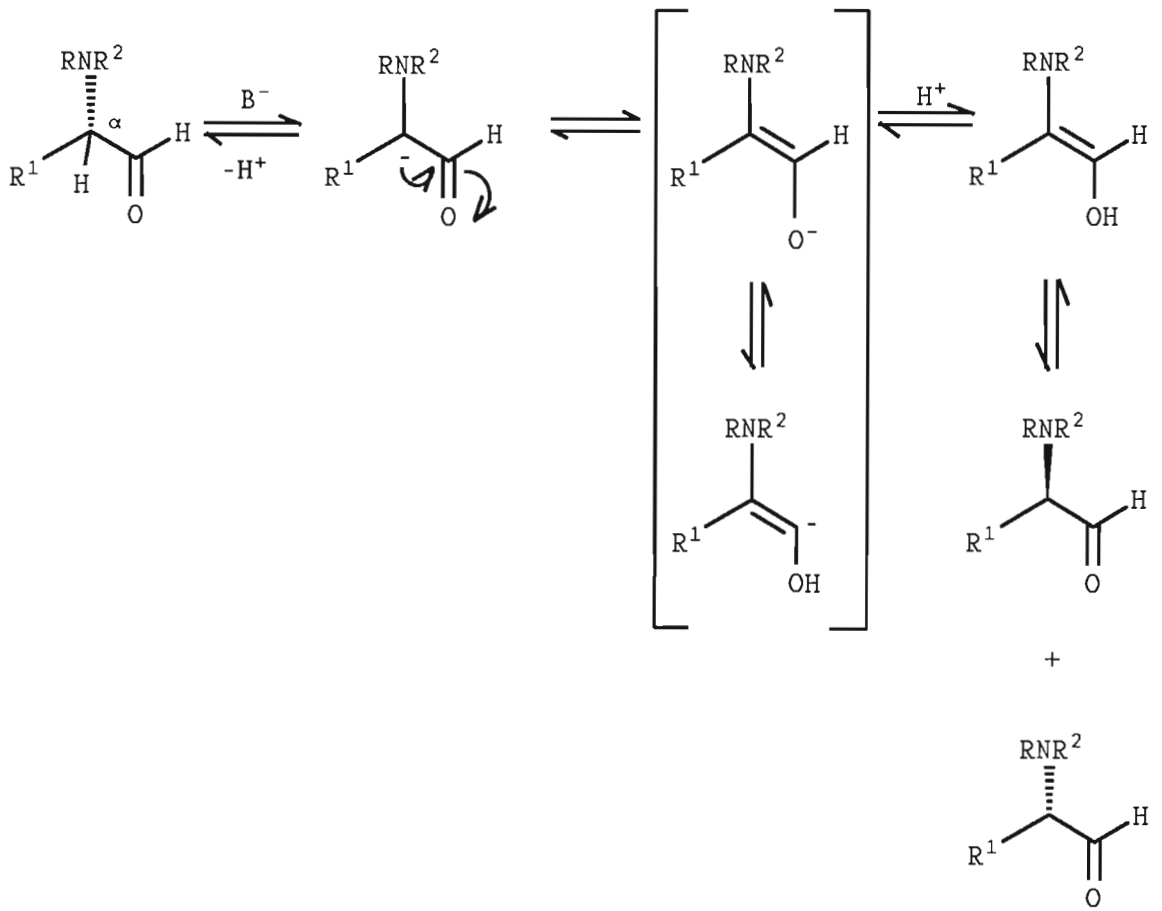
In their diastereoselective synthesis of a phosphostatine derivative, Dellaria and Maki[198] noted that a potential complication involved anion deprotonation of the amino-urethane competitively with addition to the aldehyde carbonyl (EQUATION 54).



EQUATION 54.

Thus, as in the case of the α-alkoxy aldehydes, which were reacted under the Baylis-Hillman reaction conditions, a

similar racemisation mechanism has been proposed (SCHEME 73).



SCHEME 73.

CHAPTER 4

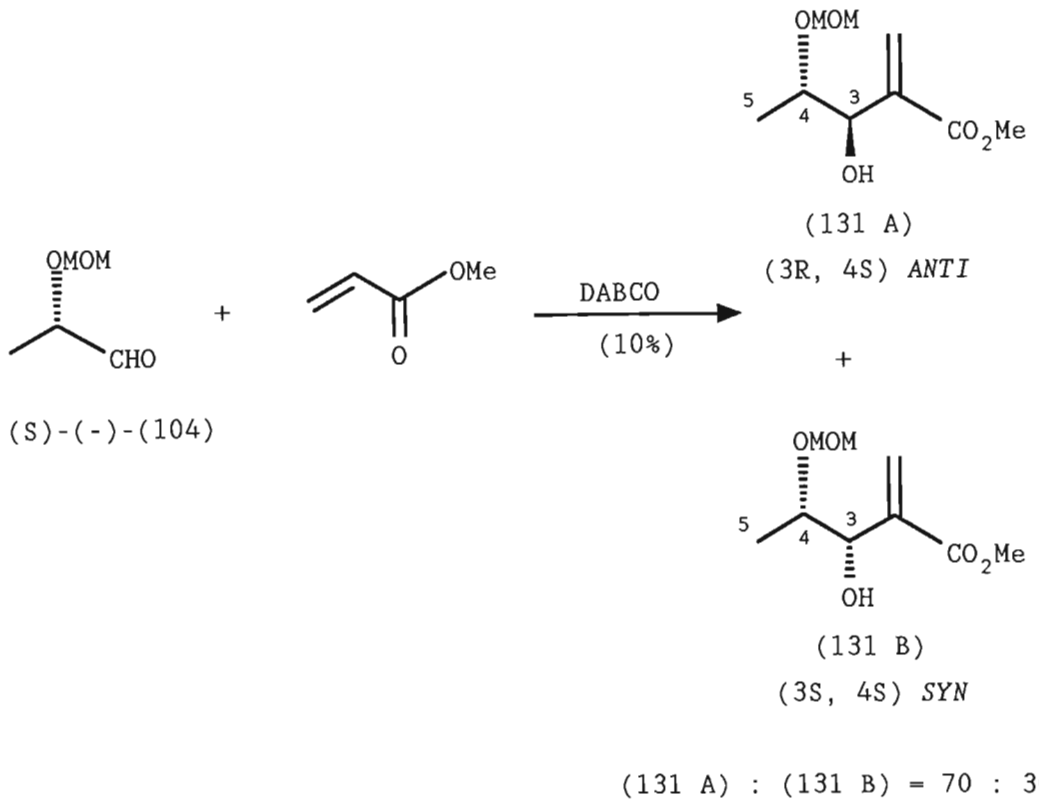
4. REACTIONS OF THE ALKOXY ALDEHYDES WITH CHIRAL ACRYLATES: PRELIMINARY ATTEMPTS AT DOUBLE DIASTEREOSELECTION.

4.1. INTRODUCTION AND PERSPECTIVE.

To date, there have been no reports on attempted double diastereoselection in the Baylis-Hillman reaction. Several authors[85-87,89,136] have however, used chiral acrylic esters with achiral aldehydes. The option of using chiral acrylic esters with chiral aldehydes in the context of double diastereoselection is a worthy undertaking.

It was thus of interest to investigate the principle of double asymmetric induction (or double stereo-differentiation) as outlined by Masamune *et al.*[57] and Heathcock *et al.*.[55]

The model aldehyde chosen for this initial study was the simple alkoxy aldehyde, (S)-(-)-2-(methoxymethoxy)propanal (104). We have observed that the inherent diastereofacial selectivity (D.S.) of this aldehyde, when utilised in optically pure form with an *achiral* acrylate (for example, methyl acrylate) is of the order 2.33:1 as shown in EQUATION 55.



(S)-(-)-(104)

(131 A) : (131 B) = 70 : 30

EQUATION 55.

Thus, the (S)-enantiomer of this aldehyde gives mainly the (RS)-aldol (*anti*) in its reaction with *achiral* enolates, (in this case the achiral vinyl component). This stereochemical assignment has been established in a previous chapter (CHAPTER 2), on the basis of the relative proton chemical shift of the C-5 methyl group which is shifted *upfield* for the *anti* diastereomer, in accordance with the published[153] data.

Bearing in mind that this was a preliminary investigation, the choice of the chiral α,β-unsaturated, β-unsubstituted, esters was limited by their availability in *both* enantiomerically pure forms.

Thus, the following chiral acrylic esters were employed

(FIGURE 61).

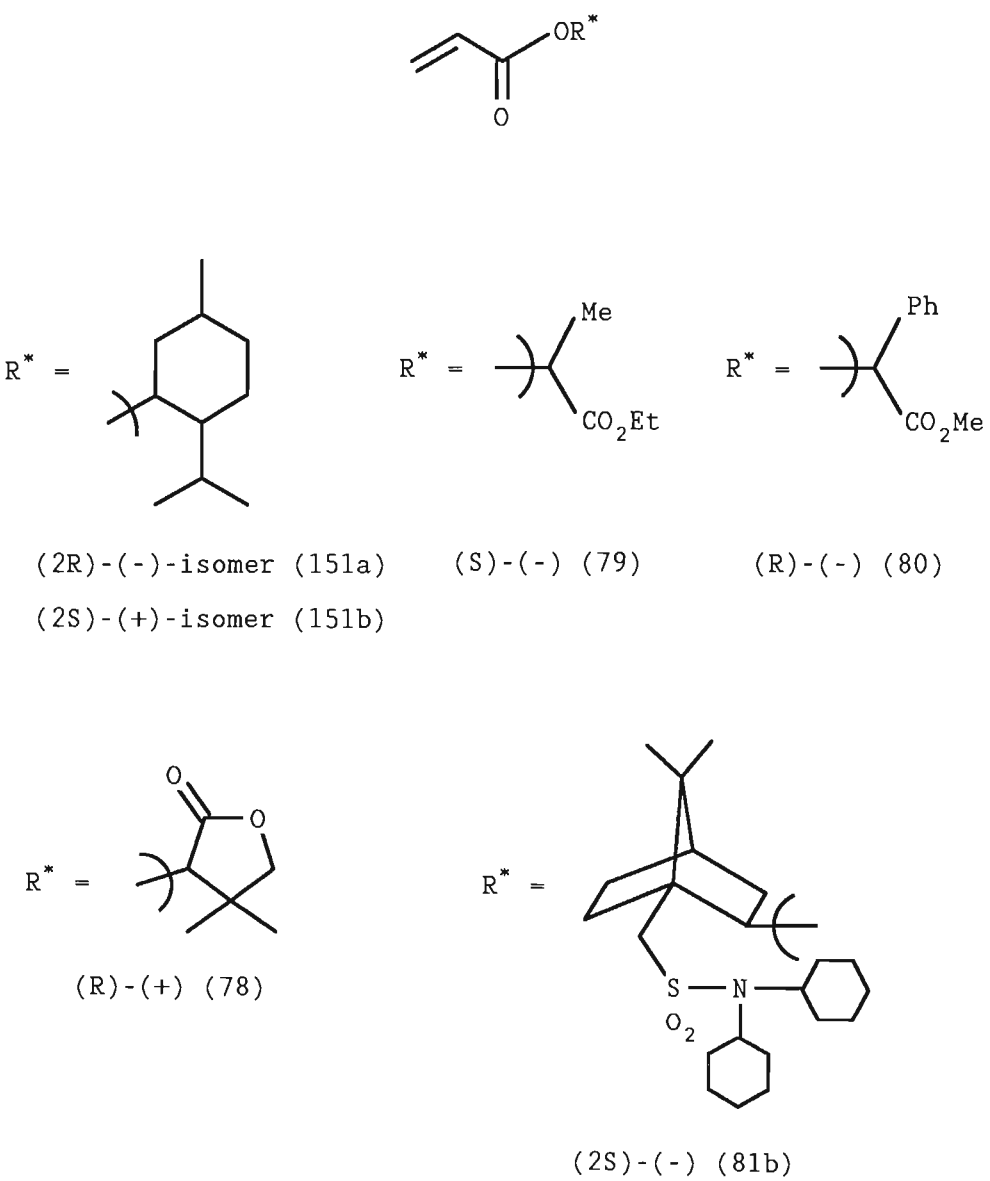
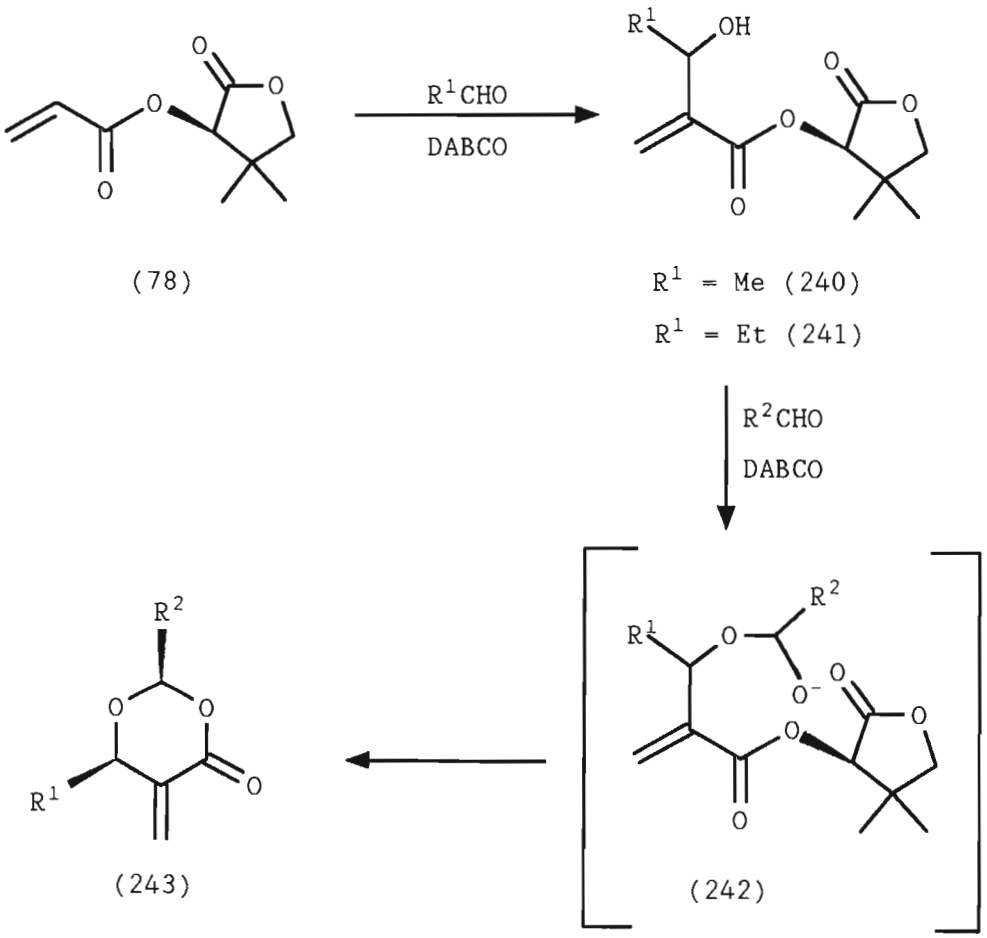


FIGURE 61.

4.2 THE CHIRAL ACRYLIC ESTERS.

4.2.1 "CYCLISATION" REACTIONS WITH ACHIRAL ALDEHYDES.

Emslie and co-workers[136] have discovered a novel cyclisation reaction during their investigations with the chiral acrylates (78)-(80), which afforded the corresponding 2,6-dialkyl-5-methylene-1,3-dioxan-4-ones (243) (SCHEME 74).



(78)

R^1 = Me (240)

R^1 = Et (241)

(242)

(243)

SCHEME 74.

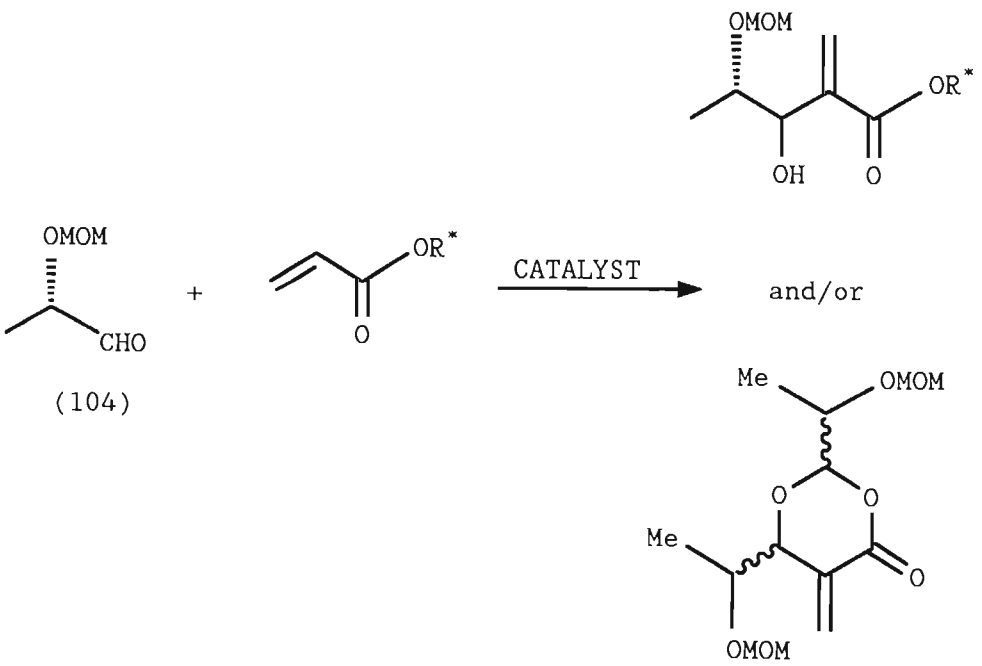
The vinyl ester (78) reacts with acetaldehyde in the usual aldol manner. However, further reaction with a *second* molecule of the aldehyde, followed by an intramolecular

transesterification, furnishes the 1,3-dioxanone (243) in high d.e..

In addition, these reactions were found to be very much faster than the classical reaction reported by Baylis and Hillman.[69]

It was also noted that a critical factor in this cyclisation is the choice of acrylate, that is, no cyclisation occurred with the usual alkyl esters (e.g., methyl and ethyl). Observed reaction times were also fast with the lactate and the mandelate-derived acrylic esters (79) and (80).

In view of the above findings, it was thus of interest to determine whether the corresponding cyclic product (244) would be formed from reaction of the chiral alkoxy aldehyde (104) with the chiral acrylic esters (EQUATION 19).



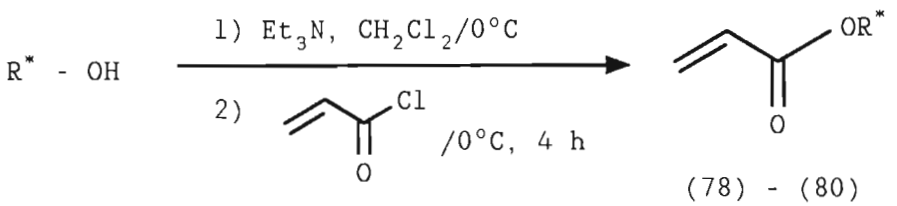
(104)

(244)

EQUATION 19.

4.2.2 PREPARATION.

Esters (78)-(80) were prepared by the known procedure.[86,123] (EQUATION 12).



(78) - (80)

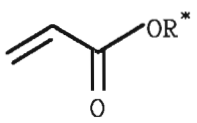
EQUATION 12.

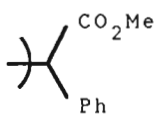
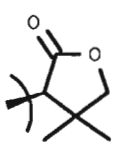
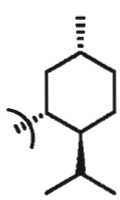
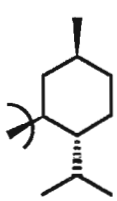
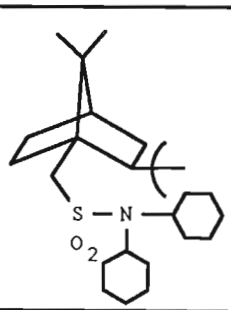
Chiral esters (81b)[87,88] and (151) were available in the research group.†

TABLE 28 summarises the data on the chiral esters employed for this investigation.

† We thank Mr. A. A. Khan and Ms. K. N. Jensen for generously providing these acrylates.

TABLE 28: The chiral acrylates.



COMPD.	R*	$[\alpha]_D$ (solvent)	ABSOLUTE CONFIGN.
79		-37.96° ($CHCl_3$)	(S)
80		-142.41° ($CHCl_3$)	(R)
78		+6.48° (CH_2Cl_2)	(R)
151a		-86.41° (dioxane)	(2R,4R,7S)
151b		+82.05° (dioxane)	(2S,4S,7R)
81b		+32.68° (Abs. EtOH)	(1R,2S,4S)

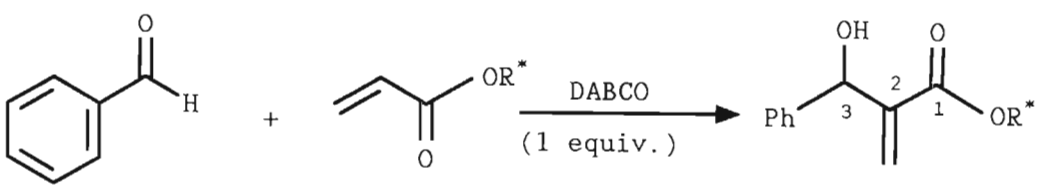
4.2.3 DETERMINATION OF THE DIASTEREOFACIAL SELECTIVITY.

For best interpretation of the double stereodifferentiation experiments, it is required to know not only the inherent diastereoface selectivity (D.S.) of the chiral partner toward the achiral partner, but also its sense (directionality).

In order for such experiments to be significant, it is necessary that both chiral reaction partners each show some diastereofacial selectivity in their reactions with achiral partners.

4.2.3.1 REACTIONS WITH BENZALDEHYDE.

For the chiral aldehyde (104) the facial selectivity was known (EQUATION 55). As a measure of the inherent diastereoface selectivity of the chiral esters, we examined the condensation of compounds (78)-(80) and (151a) with benzaldehyde (EQUATION 55).



(78) - (80)
(151a)

(245) - (249)

EQUATION 56.

The following data, concerning the asymmetric induction, was

obtained (TABLE 29).

TABLE 29: Reactions of the chiral esters with benzaldehyde.

ENTRY	ACRYLATE	RXN[a] TIME (DAYS)	PRODUCT	D.R.[d]	d.e. (%)	D.S. OF ACRYLATE
1	79	12	245	52:48	4	1.08
2	80	10	246	67:33	34	2.03
3	78	11	247	51:49	2	1.04
4	151a	14[b]	248	55:45	10[e]	1.22
5	81b	15[c]	249	–	25[c]	1.67[f]

[a]All reactions were judged incomplete by ^{1}H n.m.r.

[b]Basavaiah *et al.*[89] reports a reaction time of 7 days.

[c]As determined/reported by Basavaiah *et al.*,[89] (reaction of this acrylate was not carried out).

[d]Determined by integration of the methylene signals between 5.8 and 6.6 ppm.

[e]Basavaiah *et al.*[89] and Isaacs and co-workers[85] reported d.e.'s of 15 and 22%, respectively.

[f]Calculated from the reported[89] d.e.

The observed reaction rate (TABLE 29) is generally slow and parallels previous findings, that is, the sluggishness of

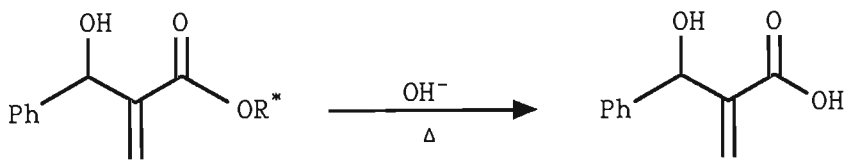
the Baylis-Hillman reaction, in general.

One can intuitively anticipate that the D.S. of the chiral reactant will critically depend on the *choice* of the *achiral* partner. This has been clearly stated by Masamune,[57] and the results obtained by both Basavaiah *et al.*[89] and Isaacs and co-workers[85] strongly support the latter prediction.

In view of the fact that this reaction establishes a 1,5-relationship (1,5-asymmetric induction), one can predict comparatively lower diastereoselectivities as compared with 1,2-asymmetric induction. The above results (TABLE 29) indicate that most of the chiral esters do not exhibit high diastereoface selectivity in their reactions with *benzaldehyde* (ratios ranging from 1.0:1 to 2.0:1.0). The ethyl lactate and pantolactone-derived acrylates (ENTRIES 1 and 2) show virtually no diastereoselectivity. For acrylate (80) however, the observed ratio is comparable to that obtained with the chiral α-alkoxy or *N*-protected α-amino aldehydes, where 1,2-induction operates. This relatively high d.e. is probably due to the "π-π stacking" effect[199] of the two phenyl moieties in the transition state.

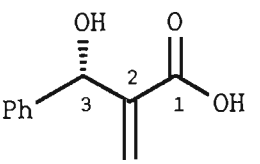
4.2.3.2 HYDROLYSIS OF THE (CHIRAL ACRYLATE-BENZALDEHYDE) CONDENSATION PRODUCTS.

In order to assign the absolute configuration of the major diastereomers in each of the mixtures (TABLE 29), we envisaged a hydrolysis to the 2-(α-hydroxy)phenyl acrylic acid (250), of known[200] absolute configuration (EQUATION 57).



(245), (246) and (248) (250a/b)

EQUATION 57.

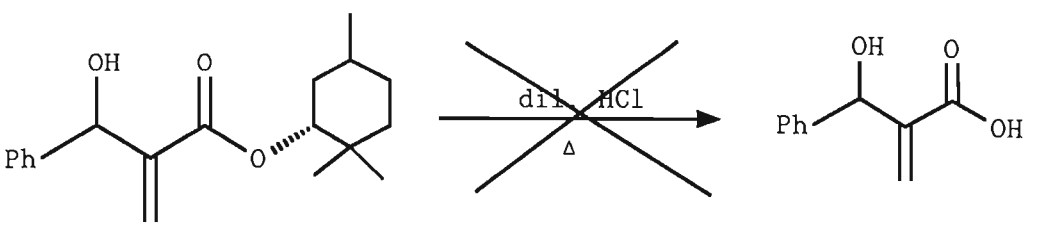


(250a)

(3R), $[\alpha]_D^{25}$ = -23.2° (c 1.05, $CHCl_3$)

It should be noted that initial acid hydrolysis of (248) was unsuccessful after a reaction time of 3 days, with quantitative isolation of starting material (EQUATION 58).

7



(248)

EQUATION 58.

Assignment of configuration at C-3 of the major diastereomers in mixtures (247) and (249) were not determined.

TABLE 30 summarises the results obtained, by inference from the observed rotations on the acids (250a/b).

TABLE 30: Hydrolysis of the coupled acrylates to the acid.

ACRYLATE	ABSOLUTE CONFIGN.	D.M.[a]	ACID	ABSOLUTE CONFIGN. OF MAJOR DIASTEREOMER AT C-3
79	(S)	245	250b	(S)
80	(R)	246	250a	(R)
151a	(R)	248	250a	(R)

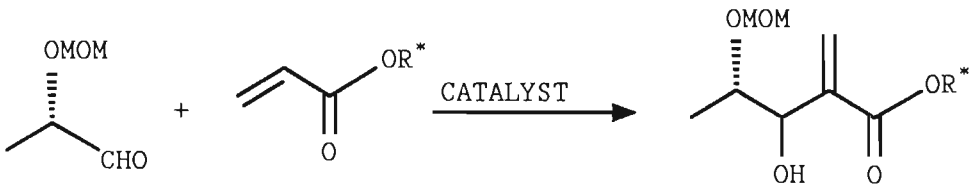
[a] Diastereomeric mixture.

Since our chiral aldehyde displays "non-Cram" selectivity in its reaction with an achiral partner (methyl acrylate) in inducing the (R)-configuration at the new chiral centre [C-3 in (131 A) (EQUATION 55)], it is therefore desirable for the chosen chiral acrylates to be also (R)-selective with respect to their induction at C-3 in the adducts (245)-(249).

However, inspection of the results obtained (TABLE 30) indicates that acrylates (80) and (151a) would be a suitable choice. Thus, at this stage, we can predict that (S)-(104) and (R)-(80)/*(R)*-(151*a*) constitute a *matched* pair, while (S)-(104) and (S)-(79) constitute a *mismatched* pair. It is therefore obvious that (S)-(104) and *(S)*-(151*b*) would constitute a *mismatched* pair.

4.2.4 REACTIONS WITH THE ALKOXY ALDEHYDE.

Coupling reactions of the chiral aldehyde (104) with the chiral esters were then carried out under the normal conditions of the Baylis-Hillman reaction (EQUATION 19).

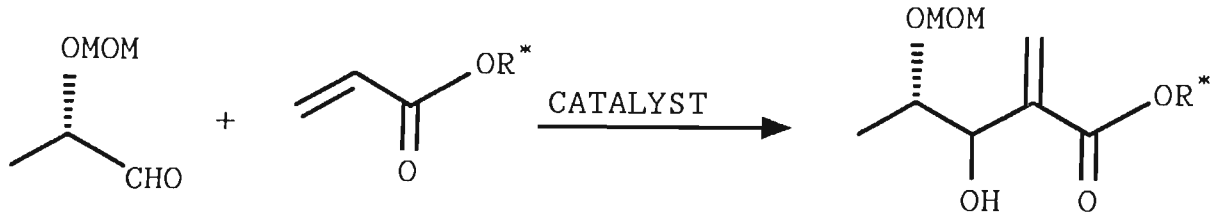


(S)-(104)

EQUATION 19.

4.2.4.1 RESULTS.

The following results were obtained (TABLE 31).



EQUATION 19.

TABLE 31: Reactions of the alkoxy aldehyde with the chiral acrylates.

ENTRY	ACRYLATE	ABSOLUTE CONFIGURATION	CATALYST (mole %)[a]	REACTION TIME[b] (d)	PRODUCT	ANTI : SYN[c] RATIO	D.S.[d]
1	79	(S)	Q (10)	4	251	68 : 32	2.13
2	79	(S)	D (20)	2	251	69 : 31	2.23
3	80	(R)	D (10)	4	252	69 : 31	2.23
4	78	(R)	D (10)	9	253	69 : 31	2.23
5	151a	(R)	D (40)	16	254a	59 : 41	1.44
6	151b	(S)	D (100)	<4	254b	65 : 35	1.86
7	81b	(R)	D (100)	>14	-	-	-

[a]Based on aldehyde.

[b]Reactions were monitored by ^{1}H n.m.r. by disappearance of the aldehyde peak.

[c]Ratio analysis was determined on the crude diastereomeric mixtures by ^{1}H n.m.r., as outlined in previous chapters.

[d]Calculated from the observed *anti*:*syn* ratios.

4.2.4.2 DISCUSSION.

It should be noted that characterisation of the products from these reactions (EQUATION 19) indicated that in all the cases studied, the corresponding cyclic products (244) were not produced.

4.2.4.2.1 REACTION RATE.

It is evident that the lactate and mandelate-derived acrylates (79) and (80) react much faster than the pantolactone- and the menthol-derived acrylic esters (154) (ENTRIES 1, 2 vs 4, 5, and 6) (TABLE 31). However, no reaction at all was observed with the camphor-sulphonic acid-derived acrylate (81b), even after prolonged reaction times. In this case, normal workup of the reaction mixture led to isolation of starting acrylate. In this respect, it should be noted that long reaction times have been observed with the "normal" (achiral) aldehydes with this acrylate. Our earlier results with the α-alkoxy aldehydes (CHAPTER 2) indicated slower reaction times than with simple aldehydes. This finding would appear to be just an additive effect that

takes it out of the useful "reaction time" range.

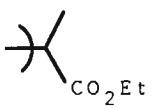
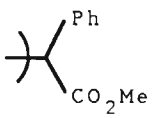
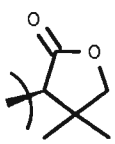
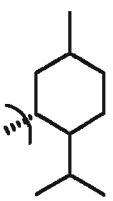
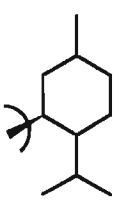
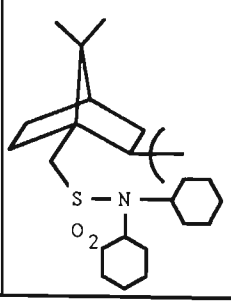
4.2.4.2.2 DIASTEREOSELECTIVITY AND D.S VALUES.

At first inspection of the *anti/syn* ratios obtained (TABLE 31), the observed diastereoselectivities are comparable to those obtained in reactions of the alkoxy aldehyde with the *achiral* acrylate/s, viz., 70:30 *anti/syn* (TABLE 5) (CHAPTER 2) on average. It thus appears that the chiral ester has virtually no effect on the diastereoselectivity. The *anti* diastereoselectivity can also be rationalised by application of the "Felkin-Anh"[30,33] model for asymmetric induction.

It is also evident that the (R)-(-)-menthyl acrylate (151a) gives a slightly lower diastereoselectivity than its corresponding enantiomer [(S)-(+)-menthyl acrylate (151b)] (ENTRIES 5 and 6), contrary to that predicted.

By application of the *multiplicative rule* for the degree of asymmetric induction, as proposed by Masamune *et al.*,[57] we can predict the approximate D.S. values for the reactions in EQUATION 19 from the corresponding D.S. values of the two chiral reactants, viz., the aldehyde (104) and the esters for each of the *matched* and *mismatched* pairs. The results of this exercise are listed in TABLE 32.

TABLE 32: Calculation of the D.S. values.

ENTRY	COMPD.	R*	D.S. (PREDICTED)[a]	
			MATCHED PAIR *axb*	MISMATCHED PAIR *a/b*
1	251		2.33x1.08 = 2.52	2.33/1.08 = 2.16
2	252		2.33x2.03 = 4.73	2.33/2.03 = 1.15
3	253		2.33x1.04 = 2.42	2.33/1.04 = 2.24
4	254a		2.33x1.22 = 2.84	2.33/1.22 = 1.91
5	254b		2.33x1.22 = 2.84	2.33/1.22 = 1.91
6	-		2.33x1.67 = 3.89	2.33/1.67 = 1.40

[A] *a* = D.S. of the chiral aldehyde

b = D.S. of the chiral ester

The D.S. obtained experimentally for (251) for the *mismatched* pair, viz., 2.23 [(TABLE 31) (ENTRIES 1, or 2)], is comparable to the value predicted, that is, 2.16 [(TABLE 32) (ENTRY 1)].

The D.S. obtained experimentally for the *matched* pairs for (252) and (254a), viz., 2.23 and 1.44 [(TABLE 31) (ENTRIES 3 and 5)], is much lower than that predicted for (252), viz., 4.73 [(TABLE 32) (ENTRY 2)] and (254a), viz., 2.84 [(TABLE 32) (ENTRY 4)].

For (254b), the predicted D.S. value for the *mismatched* pair (1.91) [(TABLE 32) (ENTRY 5)], is realised experimentally, as a D.S. value of 1.86 [(TABLE 31) (ENTRY 6)] was obtained.

For the pantolactone acrylate, the experimentally obtained D.S. value for (253), viz., 2.23 [(TABLE 31) (ENTRY 4)], is equivalent to that predicted for the *mismatched* pair, viz., 2.24 [(TABLE 32) (ENTRY 3)]. It can thus be deduced that that the (R)-pantolactone acrylate (78) induces the (S)-configuration at the new chiral centre (C-3) in the adduct (253) (EQUATION 19), opposing the (R)-induction by the chiral (S)-aldehyde (104) (*dissonant* double stereo-differentiation).

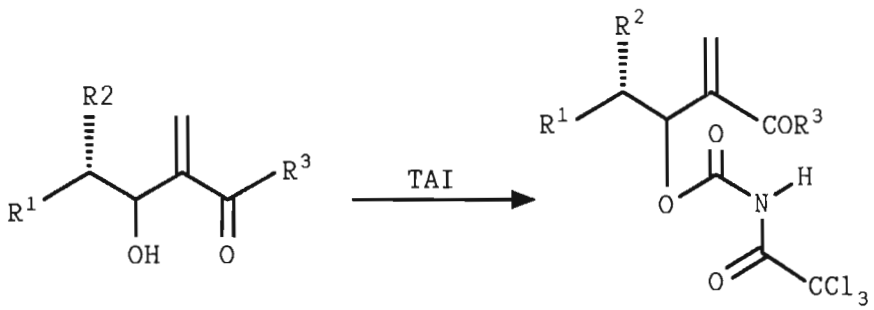
Due to the additional factor concerning the reversibility of the Baylis-Hillman reaction, the role played by the latter cannot be precluded with respect to the poor results obtained.

These preliminary results indicate that these chiral acrylates, or even their enantiomers, are not suitable chiral partners for reaction with the (S)-chiral alkoxy aldehyde (104) for achievement of the goals of double asymmetric induction/double stereodifferentiation *via* the Baylis-Hillman reaction.

4.2.4.2.3 ASSIGNMENT OF STEREOSUBSTRUCTURE.

4.2.4.2.3.1 USE OF TAI.

Stereochemical (*anti/syn*) assignments to the aldols [(251)-(254a/b)] (TABLE 31) were made on the basis of the relative carbamate shifts in the ^{1}H n.m.r. spectra of the corresponding TAI derivatives (168) (EQUATION 40).

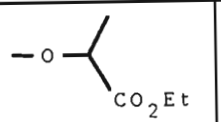
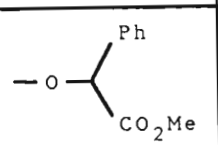
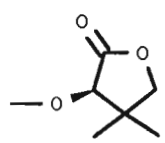
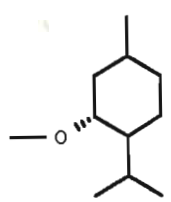
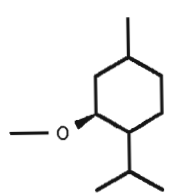


(124) (168)

EQUATION 40.

Values are listed in TABLE 33.

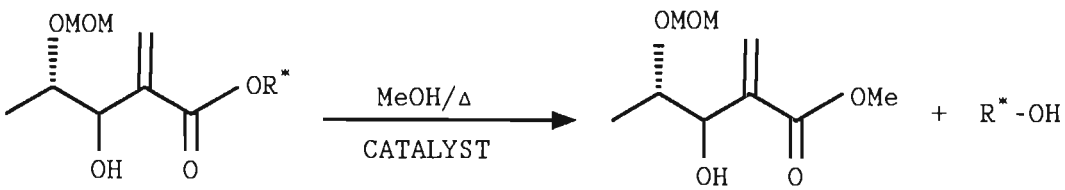
TABLE 33: Carbamate chemical shifts of the TAI derivatives (168) for the chiral aldehyde-chiral ester aldols (124).

COMPOUND	R^1	R^2	R^3	δ_{NH} (ppm)		$\delta_{SYN-ANTI}$
				SYN	*ANTI*	Δ
251	Me	OMOM		8.697	8.660	+0.037
252	Me	OMOM		8.750	8.583	+0.167
253	Me	OMOM		8.796	8.646	+0.150
254a	Me	OMOM		8.617	8.559	+0.058
254b	Me	OMOM		8.612	8.556	+0.056

The above data therefore imply that the relative configuration at the new chiral centre (C-3) is (R), in the major diastereomers of the mixtures [(251)-(254a/b)] (EQUATION 19) (TABLE 31).

4.2.4.2.3.2 TRANSESTERIFICATION STUDIES.

The above assignment of the *anti* stereosubstructure (and hence the (R)-configuration at C-3) to the major aldols in the diastereomeric mixtures [(251)-(254a/b)], was further confirmed by transesterification to the known methyl acrylic esters (131) (EQUATION 59).

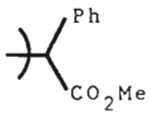
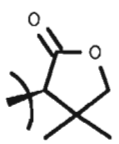
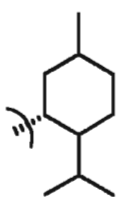
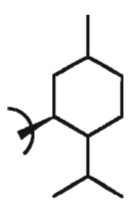


(251)-(254 a/b) (131)

EQUATION 59.

Diastereomeric ratios were again determined on these crude reaction mixtures by ^{1}H n.m.r., using previous methods. The following results were obtained (TABLE 34).

TABLE 34: Transesterification of the acrylates.

ENTRY	COMPD.	R*	CATALYST (100 MOL %)	RXN TIME (DAYS)[a]	131 *ANTI:SYN* RATIO
1	251		-	-	-
2	251		DMAP	2	-
3	251		DABCO	1[b]	67:33
4	252		DMAP	≤1	66:34
5	253		DABCO	4	-
6	253		DMAP	3	66:34
7	254a		DMAP	24	-
8	254a		$Ti(^{i}OPr)_4$	9	-
9	254b		$Ti(^{i}OPr)_4$	9	-

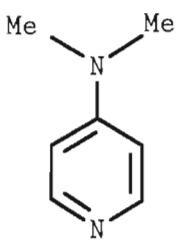
[a]Reactions were monitored by t.l.c.

[b]Reaction was 86% complete, as determined by ^{1}H n.m.r.

[c]Assignments were made by ^{1}H n.m.r. [TAI derivatisation and by virtue of the *upfield* proton chemical shift of the C-5 methyl group in the *anti* ester (131A)].

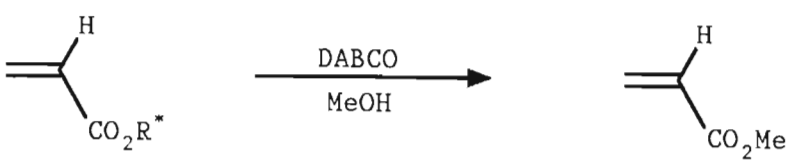
The observed diastereomeric ratios of the esters (131) (TABLE 34) are fairly consistent with those obtained for the adducts [(251)-(254a/b)] (TABLE 31) in the attempted double stereodifferentiation reactions, if one makes allowance for discrepancies due to experimental error.

For the transesterification of [(251)-(254a/b)] to the methyl esters (131), the initial choice of catalyst was 4-dimethylamino pyridine (255), since 4-dialkylamino pyridines are known[201] for their general applicability as catalysts for acylations and related reactions.

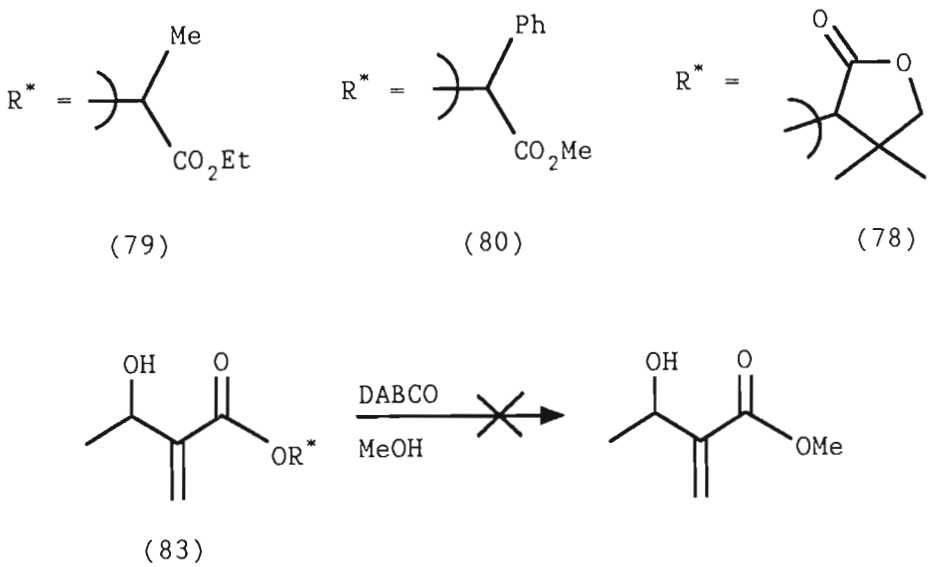


(255)

Previous studies[86] on DABCO-mediated transesterification of acrylic esters indicated that α-unsubstituted acrylates are the most susceptible to DABCO-catalysed transesterification, while α-substituted acrylates react very slowly (SCHEME 75).



(86 A)



SCHEME 75.

Some reported[86] results are presented in TABLE 35.

TABLE 35: DABCO-mediated transesterification of esters in the presence of methanol.

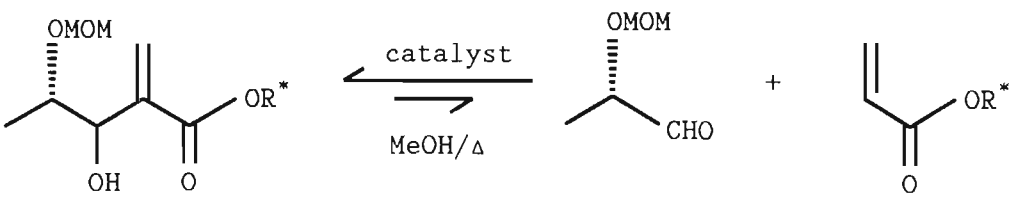
ACRYLATE	REACTION TIME	DABCO (%)	% CONVERSION
79	5 days	50	100
80	3 days	40	100
78	2 hours	10	100
83	_[a]	50	-

[a]Reaction was observed to be very slow.

Our results (TABLE 35) indicate that the relative rates of transesterification of the esters to the corresponding

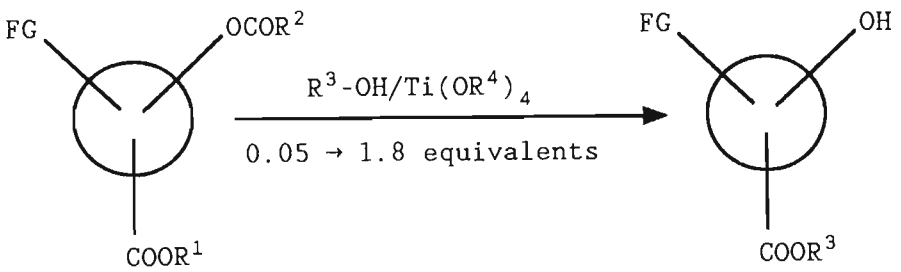
methyl esters, when catalysed by DMAP, increase in the order:
(254) > (251) > (253) > (252), with very little or no reaction in the case of the ester (251), and *no* reaction at all for ester (254a/b), even after 24 days (ENTRIES 7, 2, 6 and 4). However, the DABCO-mediated transesterifications were fairly successful for ester (251) (ENTRY 3), while no product (131) could be detected for ester (253) (ENTRY 5) after a reaction time of 4 days.

It should be noted that the use of DABCO for trans-esterification, *at that time*, was done before any possible problems of reversibility and equilibration were considered (EQUATION 60).



EQUATION 60.

An alternative, mild (neutral conditions), and selective method of transesterification is that published by Seebach,[202] in which esters of the type (256), containing additional functional groups, are treated with titanium alkoxides in alcohols as solvent (SCHEME 76).



(256) (257)

FG = functional groups such as $-Si(CH_3)_3$, $-NO_2$, -CN, -Br, -OH, -COR, conjugated or non-conjugated C=C.

SCHEME 76.

However, application of this procedure to the "menthyl-acrylates" (254a/b), even with one equivalent of catalyst, was not successful, with quantitative isolation of starting material. This investigation was not furthered.

CHAPTER 5

5. EXPERIMENTAL.

5.1 CHEMICALS AND INSTRUMENTATION.

Solvents:

All solvents were dried using standard procedures and distilled before use. $MgSO_4$ and/or Na_2SO_4 were utilised for subsequent drying of the organic layers/phases during workup, etc.

ANALYSIS/INSTRUMENTATION:

Flash column chromatography:

Was carried out using Merck silica gel (230-400 mesh) by the technique of Still *et al.*.[105]

Preparative t.l.c.:

Pre-coated MACHEREY-NAGEL TLC plates SIL G-50 UV_{254}, (0.25 mm).

Analytical t.l.c.:

Pre-coated Kieselgel 60 F_{254} Merck plastic sheets, analysed with UV-detector (254 nm), *p*-anisaldehyde "dip" reagent (465 ml EtOH: 5 ml AcOH: 13 ml H_2SO_4: 13 *p*-anisaldehyde), and also with molybdatophosphoric acid-Ce(4)sulphate spray reagent [cerium-4-sulphate (10 g) in water (940 ml) and

conc. H_2SO_4 (60 ml)] for the "amino" compounds.

Melting points:

Kofler hot-stage apparatus and are uncorrected.

Boiling points:

Not corrected.

Optical rotations:

Perkin-Elmer 241 and POLAX-D Atago polarimeters.

N.M.R. Spectra:

All chemical shifts are reported in ppm downfield from TMS as internal standard.

Where necessary, for signal detection, numbering is as shown in the text.

^{1}H n.m.r. spectra:

Varian FT 60 (60 MHz)
Varian FT 80 (80 MHz)
Gemini 200 (200 MHz)

^{13}C n.m.r. spectra:

Varian FT 80 (20 MHz)
Gemini 200 (50 MHz)

Mass spectra:

Hewlett-Packard gas chromatographic-mass spectrometer (H

P5988A) and a Varian high resolution mass spectrometer.

With respect to diastereomeric compounds, mass spectral data refer to the diastereomeric mixture, in most cases.

Diastereomeric ratios:

Initially with chiral shift reagent [Eu(FOD)] and GC/MS, but largely by ^{1}H n.m.r.

Elemental analysis:

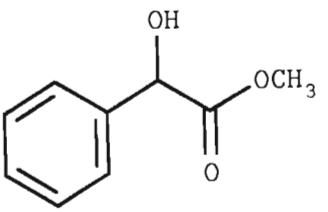
Perkin-Elmer 240B and 2400 elemental analysers.

5.2 PREPARATIONS.

5.2.1 THE α-HYDROXY ESTERS.

(±)-Methyl mandelate **(96)**

A solution of (±)-mandelic acid (20.00 g, 131.45 mmol), methanol (100 ml) and *conc.* H_2SO_4 (1.5 ml) were heated to reflux for 2 h. The mixture was cooled and the solvent removed under reduced pressure. The residue was dissolved in chloroform and sequentially washed with 2 N sodium hydrogen carbonate solution, water and brine. The organic phase was dried and concentrated. The crude ester (19.05 g, **87%**) was used without further purification. A homogenous sample was obtained by flash chromatography, using hexane-ethyl acetate (93:7) as eluant.



$C_9H_{10}O_3$ **MW** 166.18

m.p.: 53-55°C (Lit.,[203] 54-56°C).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.70 (1 H, broad s, O*H*)
3.73 (3 H, s, C*H*$_3$)
5.18 (1 H, s, C*H*OH)
7.38 (5 H, m, C$_6$*H*$_5$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

52.98 (q, *C*H$_3$)
72.92 (*C*HOH)
126.61, 128.49, 128.61 (d, *C*H aromatics)
138.26 (s, *C*CH aromatic)
174.11 (s, *C*OO)

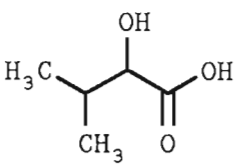
m/z (EI):

166(M^+, 71), 107(100), 89(2) and 77(31).

(±)-2-Hydroxy-3-methylbutyric acid **(97)**

A solution of sodium nitrite (36.0 g, 521.74 mmol) in water (114 ml) was added dropwise during 3 h to a stirred solution of (DL)-valine (40.0 g, 341.44 mmol) in 2 N H_2SO_4 at 0°C. The mixture was stirred for an additional 2 h at 0-5°C, then overnight at room temperature. After addition of 2 N H_2SO_4,

the clear solution was saturated with sodium chloride and extracted with diethyl ether. Removal of the solvent afforded the crude acid (25.28 g, **63%**) as a white solid, which was used without further purification. A homogenous sample was obtained by recrystallisation.



$C_5H_{10}O_3$ **MW** 118.13

m.p.: 84-87°C (from hexane-diethyl ether)
(Lit.,[204] 86-87°C).

^{1}H n.m.r. (200 MHz; CD_3OD) δ/ppm:

0.95 (3 H, d, *J* 6.8 Hz, CH_3)
1.03 (3 H, d, *J* 6.8 Hz, CH_3)
2.07 (1 H, dq, *J* 6.9 and 4.2 Hz, $CHCH_3$)
3.97 (1 H, d, *J* 4.2 Hz, CHOH)
5.07 (2 H, broad s, CHO*H* and COO*H*)

^{13}C n.m.r. (50 MHz; CD_3OD) δ/ppm:

16.87 (q, CH_3)
19.27 (q, CH_3)
33.14 (d, $CHCH_3$)
76.22 (d, CHOH)
177.42 (s, COO)

m/z (EI):

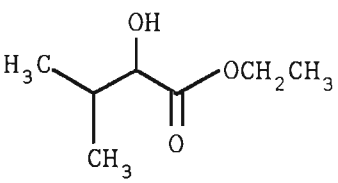
73(M^+-45, 100), 72(6), 71(7), 58(20), 55(43), 45(17) and

43(14).

$C_5H_{10}O_3$ (118.13)	Calculated: C 50.84	H 8.53
	Found: C 50.84	H 8.43

(±)-Ethyl 2-hydroxy-3-methylbutanoate **(98)**

A solution of the hydroxy acid **(97)** (24.71 g, 209.17 mmol) in 99% ethanol (175 ml), toluene (90 ml) and *conc.* hydrochloric acid (1.09 ml), was heated on a steam bath for 1.5 h, with slow removal of the solvent by distillation. The concentrated residue was diluted with 99% ethanol (88 ml) and toluene (50 ml). The solution was heated for a further 1 h, with slow removal of the solvent. The residue was fractionally distilled to afford the hydroxy ester (18.07 g, **59%**).



$C_7H_{14}O_3$ **MW** 146.19

b.p.: 171-172°C/709 mm Hg (atmospheric pressure) (Lit.,[205] 174-176°C/atmospheric pressure).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.87 (3 H, d, *J* 6.9 Hz, CH_3CH)
1.03 (3 H, d, *J* 7.0 Hz, CH_3CH)
1.31 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
2.08 (1 H, dq, *J* 6.9 and 3.6 Hz, $CHCH_3$)

2.90 (1 H, broad s, O*H*)
4.03 (1 H, d, *J* 4.0 Hz, C*H*OH)
4.26 (2 H, m, CH_2)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.27 (q, CH_3CH_2)
16.00 (q, CH_3CH)
18.80 (q, CH_3CH)
32.18 (d, $CHCH_3$)
61.54 (t, CH_2)
75.02 (d, CHOH)
174.97 (s, *C*OO)

m/z (EI):

146(M^+, 0.8), 128(0.1), 117(0.7), 104(11.9), 73(100), 58(4.8), 57(46.1), 55(16.3) and 43(4.5).

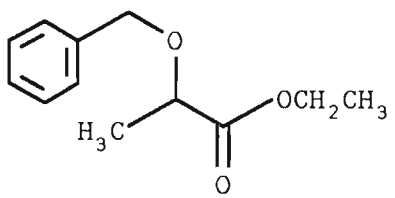
$C_7H_{14}O_3$ (146.19) Calculated: C 57.51 H 9.65
Found: C 57.63 H 9.38

5.2.2 THE *O*-PROTECTED α-HYDROXY ESTERS.

(±)-Ethyl 2-(benzyloxy)propanoate **(92)**

Sodium hydride (80% dispersion in mineral oil, 4.569 g, 152.30 mmol) was washed three times by decantation with anhydrous THF. THF (150 ml) was then added and the suspension cooled to 0°C. A solution of (±)-ethyl lactate **(87)** (15.00 g, 126.98 mmol) in THF (30 ml) was added dropwise.

The reaction mixture was stirred at room temperature for 30 min., treated with benzyl bromide (18.50 ml, 155.54 mmol) dropwise and refluxed for 2 h. The cooled mixture was quenched with a saturated solution of $NaHCO_3$ and diluted with diethyl ether. The mixture was filtered through a Celite cake and the precipitate was thoroughly washed with ether. The organic phase was separated, dried and concentrated under reduced pressure to give the crude product which was purified by vacuum distillation. This afforded the title compound (23.00 g, **87%**).



$C_{12}H_{16}O_3$ **MW** 208.26

b.p.: 98-100°C/1.2 mm Hg (Lit.,[206] 98-100°C/0.9 mm Hg).

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.25 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.41 (3 H, d, *J* 6.8 Hz, CH_3CH)
4.03 (1 H, q, *J* 7.0 Hz, $CHCH_3$)
4.19 (2 H, q, *J* 7.1 Hz, CH_2CH_3)
4.40 and 4.69 (2 H, AB system, J_{AB} 12.3 Hz, OCH_2Ph)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.25 (q, CH_3CH_2)
18.72 (q, CH_3CH)
60.83 (t, OCH_2CH_3)

71.97 (t, OCH_2Ph)
74.04 (d, $CHCH_3$)
127.82, 127.96, 128.41, (d, CH aromatics),
137.59 (s, CCH_2 aromatic)
173.25 (s, COO)

m/z (EI):

135(M^+-73, 3), 102(42), 91(100) and 74(11).

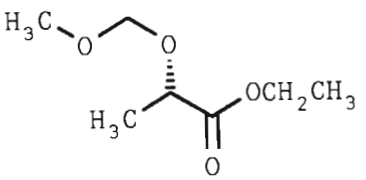
GENERAL PROCEDURE 1(A):

MOM-Protection of the α-hydroxy esters.

A solution of the α-hydroxy ester (1 equivalent) in anhydrous dichloromethane (70 ml/50 mmol) was treated at 0°C with chloromethyl methyl ether (1.54 equivalents) and *N*,*N*-diisopropylethylamine (2.25 equivalents). The mixture was stirred overnight at room temperature, then quenched with dilute hydrochloric acid (2 N) to pH 1-2. The aqueous phase was extracted with dichloromethane. The combined organic phase was washed with water to neutrality, dried and concentrated under reduced pressure. The crude product was purified by distillation.

(S)-(-)-Ethyl 2-(methoxymethoxy)propanoate **(99)**

Application of **GENERAL PROCEDURE 1(A)** to (S)-(-)-ethyl lactate **(87a)** (5.91 g, 50.03 mmol) afforded the title compound (6.46 g, **80%**).



$C_7H_{14}O_4$ **MW** 162.18

b.p.: 28-30°C/2.4 mm Hg (Lit.,[68] b.p. 179-181°C).

$[\alpha]_D^{34.6}$: -83.67° (*c* 0.60, CH_2Cl_2) [Lit.,[68] $[\alpha]_D$ -84° (*c* 1.6, CH_2Cl_2)].

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.28 (3 H, t, *J* 7.2 Hz, CH_3CH_2)
1.43 (3 H, d, *J* 6.9 Hz, CH_3CH)
3.38 (3 H, s, CH_3O)
4.21 (3 H, q, *J* 7.2 Hz, $CHCH_3$ and CH_2CH_3)
4.69 (2 H, s, OCH_2O)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

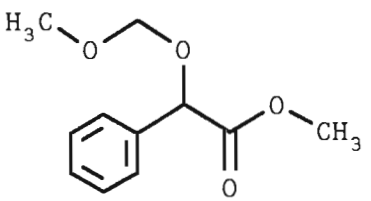
14.20 (q, CH_3CH_2)
18.56 (q, CH_3CH)
55.80 (q, CH_3O)
60.87 (t, CH_2CH_3)
71.61 (d, $CHCH_3$)
95.92 (t, OCH_2O)
173.03 (s, COO)

m/z (EI):

161(M^+-1, 0.1), 131(3.7), 117(0.5), 102(6.8), 89(33.9), 88(24.0), 73(4.8), 59(10.1), 45(100) and 43(7.0).

(±)-Methyl 2-(methoxymethoxy)-2-phenylethanoate **(101)**

Application of **GENERAL PROCEDURE 1(A)** to (±)-methyl mandelate **(96)** (5.0 g, 30.09 mmol) afforded the title compound (5.09 g, **81%**).



$C_{11}H_{14}O_4$ **MW** 210.23

b.p.: 90-93°C/0.9 mm Hg.

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:
3.39 (3 H, s, CH_3OCH_2)
3.71 (3 H, s, $COOCH_3$)
4.69 and 4.75 (2 H, AB system, J_{AB} 6.9 Hz, CH_2)
5.19 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

52.51 (q, $COOCH_3$)
56.14 (q, CH_3OCH_2)
76.84 (d, CHCO)
95.22 (t, CH_2)
127.81, 129.06, 129.16 (d, CH aromatics)
136.45 (s, CCH aromatic)
171.75 (s, COO)

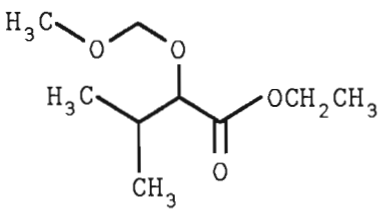
m/z (EI):

210(M^+, 0.9), 179(1.2), 151(87.8), 150(4.0), 121(30.0), 89(14.0), 77(29.1), 65(2.0), 59(1.9) and 45(100).

$C_{11}H_{14}O_4$ (210.23) Calculated: C 62.85 H 6.71
Found: C 62.76 H 6.65

(±)-Ethyl 2-(methoxymethoxy)-3-methylbutanoate **(102)**

Application of **GENERAL PROCEDURE 1(A)** to the hydroxy ester **(98)** (10.50 g, 71.92 mmol) afforded the title compound (10.12 g, **74%**).



$C_9H_{18}O_4$ **MW** 190.24

b.p.: 110-114°C/27.95 mm Hg.

^{1}**H n.m.r.** (200 MHz; $CDCl_3$) δ/ppm:

0.98 (3 H, d, *J* 6.8 Hz, CH_3CH)
1.00 (3 H, d, *J* 6.9 Hz, CH_3CH)
1.29 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
2.11(1 H, m, $CHCH_3$)
3.36 (3 H, s, CH_3O)
3.87 (1 H, d, *J* 5.5 Hz, CHCO)
4.22 (2 H, q, *J* 7.1 Hz, CH_2CH_3)
4.65 and 4.70 (2 H, AB system, J_{AB} 7.0 Hz, OCH_2O)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.29 (q, CH_3CH_2)
17.61 (q, CH_3CH)
18.81 (q, CH_3CH)
31.40 (d, $CHCH_3$)
56.04 (q, CH_3O)
60.67 (t, CH_2CH_3)
80.71 (d, CHCO)
96.42 (t, OCH_2O)
172.32 (s, COO)

m/z (EI):

161(M^+-29, 0.1), 159(6.7), 145(0.4), 130(11.3), 117(99.1), 115(17.6), 71(25.8), 56(8.8), 45(100) and 43(13.8).

$C_9H_{18}O_4$ (190.24) Calculated: C 56.82 H 9.54
Found: C 57.02 H 9.22

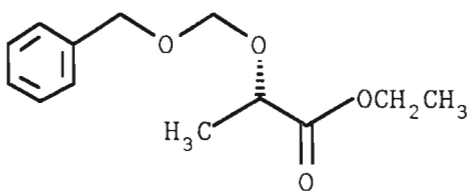
GENERAL PROCEDURE 1(B):

BOM-Protection of the α-hydroxy esters.

A solution of the α-hydroxy ester (1 equivalent) in anhydrous dichloromethane (50 ml/85 mmol) was treated at 0°C with benzyl chloromethyl ether (1.15 equivalents) and *N*,*N*-diisopropylethylamine (1.46 equivalents). The mixture was stirred overnight at room temperature. Removal of the solvent under reduced pressure afforded an oil which was purified by flash chromatography.

(S)-(-)-Ethyl 2-[(benzyloxy)methoxy]propanoate **(100)**

Application of **GENERAL PROCEDURE 1(B)** to (S)-(-)-ethyl lactate **(87a)** (10.00 g, 84.65 mmol), using hexane-ethyl acetate (95:5) as eluant, afforded the title compound (9.88 g, **49%**).



$C_{13}H_{18}O_4$ **MW** 238.29

$[\alpha]_D^{26.2}$: -44.59° (*c* 0.68, 95% EtOH) [Lit.,[68] $[\alpha]_D$ -48.3° (*c* 1.73, EtOH)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.25 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.43 (3 H, d, *J* 7.0 Hz, CH_3CH)
4.16 (2 H, q, *J* 7.1 Hz, CH_2CH_3)
4.26 (1 H, q, *J* 7.0 Hz, $CHCH_3$)
4.64 (2 H, s, CH_2Ph)
4.83 (2 H, s, OCH_2O)
7.33 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.15 (q, CH_3CH_2)
18.55 (q, CH_3CH)
60.91 (t, CH_2CH_3)
69.92 (t, CH_2Ph)
71.68 (d, $CHCH_3$)

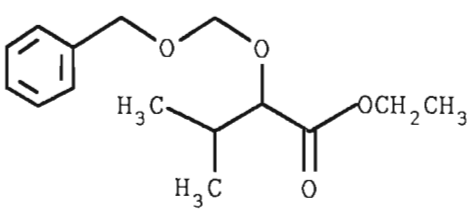
93.95 (t, OCH_2O)
127.73, 127.85, 128.41 (d, *C*H aromatics)
137.66 (s, CCH_2 aromatic)
173.05 (s, *C*OO)

m/z (EI):

209(M^+-29, 0.2), 165(0.8), 164(0.2), 131(2.2), 120(18.5), 103(), 91(100), 77(5.5), 65(12), 45(2.2), 44(1.0) and 43(3.6).

(±)-Ethyl 2-[(benzyloxy)methoxy]-3-methylbutanoate **(103)**

Application of **GENERAL PROCEDURE 1(B)** to the hydroxy ester **(98)** (5.0 g, 34.25 mmol), using hexane-ethyl acetate (93:7) as eluant, afforded the title compound (7.98 g, **88%**).



$C_{15}H_{22}O_4$ **MW** 266.34

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.99 (3 H, d, *J* 6.8 Hz, CH_3CH)
1.01 (3 H, d, *J* 6.8 Hz, CH_3CH)
1.25 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
2.13 (1 H, dq, *J* 6.8 and 5.4 Hz, $CHCH_3$)
3.96 (1 H, d, *J* 5.5 Hz, *C*HO)
4.17 (2 H, q, *J* 7.2 Hz, CH_2CH_3)

4.64 (2 H, s, CH_2Ph)
4.81, (2 H, s, OCH_2O)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.25 (q, CH_3CH_2)
17.65 (q, CH_3CH)
18.84 (q, CH_3CH)
31.45 (d, $CHCH_3$)
60.66 (t, CH_2CH_3)
69.95 (t, CH_2Ph)
80.92 (d, CHO)
94.50 (t, OCH_2O)
127.71, 127.81, 129.39 (d, CH aromatics)
137.64 (s, CCH_2 aromatic)
172.28 (s, CO)

m/z (EI):

237(M^+-29, 0.04), 221(0.02), 193(0.82), 115(7.78), 91(100), 77(2.99), 65(9.78), and 45(0.44).

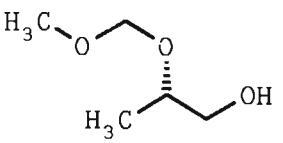
$C_{15}H_{22}O_4$ (266.34) Calculated: C 67.65 H 8.33
Found: C 68.07 H 8.57

5.2.3 THE α-ALKOXY ALCOHOL.

(S)-(+)-2-(Methoxymethoxy)propanol **(109)**

A solution of the ester **(99)** (21.85 g, 134.88 mmol) in anhydrous THF (220 ml) was added dropwise to a suspension of

lithium aluminium hydride (5.45 g, 143.61 mmol) in THF (145 ml). After stirring at room temperature for 10 min., the reaction mixture was quenched by sequential treatment with ethyl acetate (11.11ml, 144 mmol) and 10% aqueous KOH (33 ml). The mixture was stirred for a further 30 min., the resulting precipitate filtered off and thoroughly washed with diethyl ether. Evaporation of the filtrate under reduced pressure afforded the pure alcohol (13.59 g, **84%**).



$C_5H_{12}O_3$ **MW** 120.15

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.17 (3 H, d, *J* 6.4 Hz, CH_3CH)
2.95 (1 H, broad s, O*H*)
3.42 (3 H, s, CH_3O)
3.54 (2 H, d, *J* 3.2 Hz, CH_2OH)
3.77 (1 H, tq, *J* 6.6 and 3.1 Hz, $CHCH_3$)
4.72 (2 H, AB system, J_{AB} 6.9 Hz, OCH_2O)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.04 (q, CH_3CH)
55.48 (q, CH_3O)
66.94 (t, CH_2OH)
76.70 (d, *C*H)
96.09 (t, OCH_2O)

m/z (EI):

119(M^+-1, 9), 90(10), 89(90), 75(15), 59(35), 45(100) and

43(8).

5.2.4 THE ALKOXY ALDEHYDES.

5.2.4.1 THE α-ALKOXY ALDEHYDES.

GENERAL PROCEDURE 2:

Reduction of the O-protected esters with DIBAL-H.

A solution of the α-alkoxy ester (1 equivalent) in anhydrous *n*-hexane (47 ml/12 mmol), was treated at -90°C with a 1.0 M solution of diisobutylaluminium hydride (1.02 equivalents) in *n*-hexane. After 10 min., the reaction was quenched with a saturated solution of aqueous ammonium chloride, diluted with diethyl ether and filtered through a Celite cake. The organic phase was dried and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography and/or distillation.

GENERAL PROCEDURE 3:

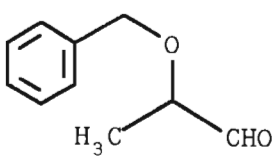
Swern oxidation of the α-alkoxy, (or *N*-protected, α-amino) alcohol.

Dimethyl sulfoxide (2.01 equivalents) was added to a cooled (-60°C) solution of oxalyl chloride (1.21 equivalents) in anhydrous dichloromethane (550 ml/37 mmol oxalyl chloride).

The mixture was stirred for 5 min.. A solution of the alcohol (1 equivalent) in anhydrous dichloromethane was added dropwise and the mixture was stirred for 45 min.. Triethylamine (4.03 equivalents) was then added. Water was added after 10 min. and the reaction mixture allowed to attain room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was successively washed with dilute (1%) hydrochloric acid (160 ml/17 ml Et_3N), water (160 ml), dilute (5%) sodium hydrogen carbonate solution (160 ml) and brine. After drying the organic layer, concentration under reduced pressure afforded the crude product, which was either used without further purification, or was purified by flash chromatography.

(±)-2-(Benzyloxy)propanal **(11)**

Application of **GENERAL PROCEDURE 2** to the ester **(92)** (3.00 g, 14.42 mmol), using hexane-ethyl acetate (70:30) as eluant, afforded the title compound (0.83 g, **35%**).



$C_{10}H_{12}O_2$ **MW** 164.21

b.p.: 73-75°C/1.5 mm Hg.

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.30 (3 H, d, *J* 6.9 Hz, CH_3CH)

3.82 (1 H, dq, *J* 6.9 and 1.7 Hz, $CHCH_3$)
4.59 (2 H, s, CH_2O)
7.30 (5 H, m, C_6H_5)
9.63 (1 H, d, *J* 1.7 Hz, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.34 (q, CH_3)
72.22 (t, CH_2)
79.65 (d, $CHCH_3$)
128.32, 128.46, 128.95 (d, CH aromatics)
137.71 (s, CH_2C aromatic)
204.07 (d, CHCHO)

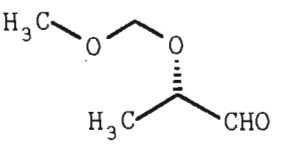
m/z (EI):

135(M^+-29, 26), 107(7), 92(10), 91(100), 77(2) and 65(6).

(S)-(-)-2-(Methoxymethoxy)propanal **(104)**

Application of **GENERAL PROCEDURE 2** to the ester **(99)** (2.0g, 12.35 mmol), using pentane-acetone as eluant (80:20), afforded the title compound (0.51 g, **35%**).

Application of **GENERAL PROCEDURE 3** to the alcohol **(109)** (10.84 g, 90.33 mmol), using pentane-acetone (80:20) as eluant, afforded the title compound (2.79 g, **26%**).



$C_5H_{10}O_3$ **MW** 118.13

$[\alpha]_D^{rt}$: -12.55° (*c* 0.55, $CHCl_3$) [Lit.,[68] $[\alpha]_D$ -12.6° (*c* 1.6, $CHCl_3$)].

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

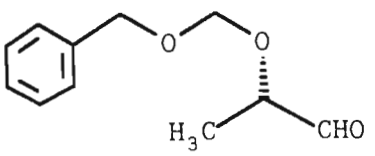
1.32 (3 H, d, *J* 7.0 Hz, CH_3CH)
3.41 (3 H, s, CH_3O)
4.03 (1 H, dq, *J* 1.6 and 7.0 Hz, $CHCH_3$)
4.73 (2 H, s, CH_2)
9.64 (1 H, d, *J* 1.7 Hz, CHCHO)

m/z (EI):

117(M^+-1, 0.1), 89(32.8), 74(0.4), 59(30.0), 58(3.0), 57(9.3), 45(100) and 1(7.2).

(S)-(-)-2-[(Benzyloxy)methoxy]propanal **(105)**

Application of **GENERAL PROCEDURE 2** to the ester **(100)** (2.84 g, 11.93 mmol), using hexane-ethyl acetate (85:15) as eluant, afforded the title compound (1.51 g, **65%**).



$C_{11}H_{14}O_3$ **MW** 194.23

[α]$_D^{rt}$: -7.66° (*c* 1.31, $CHCl_3$) [Lit.,[68] [α]$_D$ -13.4° (*c* 1.6, $CHCl_3$)].

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.23 (3 H, d, *J* 7.0 Hz, CH_3)
4.00 (1 H, dq, *J* 7.0 and 1.5 Hz, $CHCH_3$)
4.58 (2 H, s, CH_2Ph)
4.77 (2 H, s, OCH_2O)
7.27 (5 H, s, C_6H_5)
9.54 (1 H, d, *J* 1.5 Hz, CHCHO)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

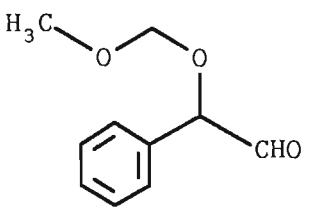
15.28 (q, CH_3)
70.08 (t, CH_2Ph)
78.19 (d, $CHCH_3$)
94.20 (t, OCH_2O)
127.85, 127.90, 128.53 (d, CH aromatics)
137.39 (s, CCH_2 aromatic)
202.42 (d, CHCHO)

m/z (EI):

165(M^+-29, 1), 164(1), 136(1), 120(2), 92(10), 91(100), 77(3), 65(6), 58(2) and 45(1).

(±)-2-(Methoxymethoxy)-2-phenylethanal **(106)**

Application of **GENERAL PROCEDURE 2** to the ester **(101)** (2.14 g, 10.19 mmol) in anhydrous *diethyl ether* (90 ml), (reaction time: *50* min.), afforded the title compound (1.05 g, **57%**).



$C_{10}H_{12}O_3$ **MW** 180.21

b.p.: 88-89°C/1.6 mm Hg.

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

3.39 (3 H, s, CH_3)
4.75 (2 H, s, CH_2)
5.03 (1H, d, *J* 1.7 Hz, C*H*Ph)
7.37 (5 H, s, C_6H_5)
9.60 (1 H, d, *J* 1.7 Hz, CHC*H*O)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

56.16 (q, CH_3)
83.40 (d, *C*HPh)
95.46 (t, CH_2)
127.99, 129.34, 129.41 (d, *C*H aromatics)
133.87 (s, *C*CH aromatic)
198.46 (d, CH*C*HO)

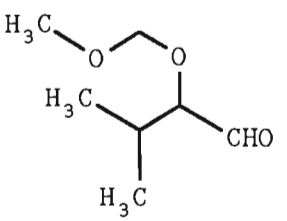
m/z (EI):

151(M^+-29, 60), 121(9), 120(2), 106(5), 105(43), 91(62), 77(53), 65(19), 45(100) and 31(3).

$C_{10}H_{12}O_3$ (180.21) Calculated: C 66.65 H 6.71
Found: No satisfactory analysis.

(±)-2-(Methoxymethoxy)-3-methylbutanal **(107)**

Application of **GENERAL PROCEDURE 2** to the ester **(102)** (3.00 g, 15.79 mmol), using hexane-acetone (96:4) as eluant, afforded the title compound (0.74 g, **32%**).



$C_7H_{14}O_3$ **MW** 146.18

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.00 (3 H, d, *J* 6.8 Hz, CH_3CH)
1.02 (3 H, d, *J* 6.9 Hz, CH_3CH)
2.12 (1 H, dq, *J* 6.9 and 5.4 Hz, $CHCH_3$)
3.42 (3 H, s, CH_3O)
3.67 (1 H, dd, *J* 5.3 and 2.4 Hz, $CHOCH_2$)
4.68 and 4.74 (2 H, AB system, J_{AB} 6.8 Hz, CH_2)
9.64 (1 H, d, *J* 2.4 Hz, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.39 (q, CH_3CH)
18.58 (q, CH_3CH)

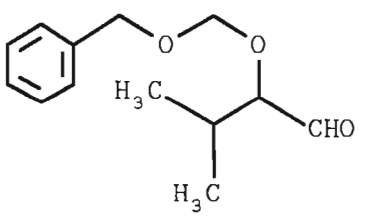
29.87 (d, $CHCH_3$)
55.99 (q, CH_3O)
86.86 (d, $CHOCH_2$)
97.01 (t, CH_2)
203.59 (d, CHCHO)

m/z (EI):
145(M^+-1, 0.1), 117(83.4), 85(10.6), 72(2.5), 71(27.6), 57(7.7), 45(100) and 43(7.2).

$\mathbf{C_7H_{14}O_3}$ (146.18) Calculated: C 57.53 H 9.66
Found: Unstable to analysis.

(±)-2-[(Benzyloxy)methoxy]-3-methylbutanal **(108)**

Application of **GENERAL PROCEDURE 2** to the ester **(103)** (3.00 g, 11.28 mmol), using hexane-ethyl acetate (93:7) as eluant, afforded the title compound (1.39 g, **56%**).



$C_{13}H_{18}O_3$ **MW** 222.29

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.00 (3 H, d, *J* 6.9 Hz, CH_3)
1.03 (d, *J* 6.9 Hz, CH_3)
2.12 (1 H, dq, *J* 6.8 and 5.3 Hz, $CHCH_3$)
3.76 (1 H, dd, *J* 5.3 and 2.2 Hz, $CHOCH_2$)

4.63 and 4.70 (2 H, AB system, J_{AB} 11.7 Hz, OCH_2O)
7.34 (5 H, m, C_6H_5)
9.66 (1 H, d, J 2.2 Hz, CHC*H*O)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.39 (q, CH_3)
18.62 (q, CH_3)
29.89 (d, $CHCH_3$)
70.05 (t, CH_2Ph)
86.84 (d, $CHOCH_2$)
94.97 (t, CH_2O)
127.80, 127.84, 128.48 (d, *C*H aromatics)
137.32 (s, CCH_2 aromatic)
203.36 (d, CHCHO)

m/z (EI):

193(M^+-29, 1.3), 163(5.0), 91(100), 86(2.0), 85(2.0), 77(2.0), 71(2.0), 65(5.0).

m/z (CI; CH_4):

223(MH^+, 2), 221(2), 193(89), 163(5), 131(100).

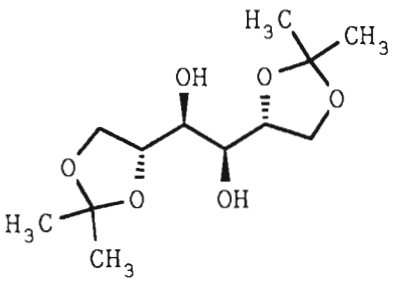
$C_{13}H_{18}O_3$ (222.29) Calculated: C 70.25 H 8.16
Found: C 70.03 H 8.25

5.2.4.2 THE α,β-DIALKOXY ALDEHYDES.

5.2.4.2.1 ISOPROPYLIDENEGLYCERALDEHYDE.

1,2-5,6-Isopropylidene-(D)-mannitol **(117)**

Zinc chloride (80 g, 587.03 mmol) was dissolved in anhydrous acetone (400 ml). After the insoluble residue had settled out, the supernatant liquid was decanted into (D)-mannitol **(116)** (50 g, 274.47 mmol). The resulting mixture was mechanically stirred, under anhydrous conditions, for 2 h. The solution was filtered and the filtrate rapidly added to an effficiently stirred, (mechanically), mixture of anhydrous K_2CO_3 (100 g, 723.54 mmol) in water (100 ml) and diethyl ether (400 ml). After continued stirring for 40 min., the acetone-ether solution was decanted and the zinc carbonate pellets thoroughly washed with acetone-diethyl ether solution (1:1 v/v, 120 ml). The combined solution was dried by stirring with calcined K_2CO_3 (100 g) for 30 min. The solution was filtered and the carbonate washed with acetone-ether solution (1:1 v/v, 120 ml). The combined filtrate and washings were evaporated under reduced pressure. The residue was dried *in vacuo* at 60-70°C (water bath) for 2 h. *n*-Butyl ether (120 ml) was then added to the residue. The mixture was heated on an oil bath to 135°C. The resulting hot solution was rapidly filtered. The filtrate was cooled in ice. The solid product was filtered off, washed with low-boiling petroleum ether, and dried *in vacuo* to afford the title compound (23.7 g, **33%**), which was used without further purification.



$C_{12}H_{22}O_6$ **MW** 262.31

m.p.: 115-116°C (Lit.,[117] 117-119°C).

A sample was recrystallised (from water) for analytical purposes.

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:
1.36 (6 H, s, 2 × C*H*$_3$)
1.42 (6 H, s, 2 × C*H*$_3$)
2.84 (2 H, d, *J* 6.9 Hz, 2 × CHO*H*)
3.74 (2 H, m, 2 × C*H*CH$_2$)
4.00 (2 H, m, 2 × C*H*OH)
4.08-4.19 (4 H, m, 2 × C*H*$_2$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.28, 26.82 (q, *C*H$_3$)
66.93 (t, *C*H$_2$)
71.29 (d, *C*HOH)
76.63 (d, *C*HCH$_2$)
109.69 (s, O*C*O)

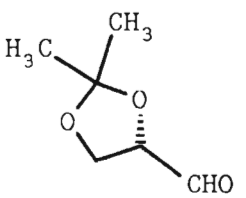
m/z (EI):

247(M^+-15, 7), 229(3), 131(7), 129(6), 101(100), 85(9), 83(8), 43(29), 71(3) and 69(8).

$C_{12}H_{22}O_6$ (262.31) Calculated: C 54.95 H 8.45
Found: C 55.04 H 8.44

(R)-2,3-O-Isopropylideneglyceraldehyde **(20)**

The diol **(117)** (3.29 g, 12.56 mmol) was dissolved in anhydrous dichloromethane (33 ml). The flask was maintained at 25°C (water bath). Sodium *meta*-periodate (5.37 g, 25.12 mmol) was added with vigorous stirring. Distilled water (1.32 ml) was then added, and stirring was continued for 1.5 h. $MgSO_4$ (5.58 g) was added and stirring was continued for 15 min. The reaction mixture was filtered off and the solids were rinsed with dichloromethane (14 ml). The solvent was removed under reduced pressure and distillation of the residual oil afforded the pure aldehyde (1.53 g, **47%**).



$C_6H_{10}O_3$ **MW** 130.15

b.p.: 45-47°C/14 mm Hg (Lit.,[116] 60-62°C/20 mm Hg).

$[\alpha]_D^{25}$: +65.53° (*c* 1.22, C_6H_6) [Lit.,[207] $[\alpha]_D$ +64.9° (*c* 5.73, C_6H_6)].

^{1}H n.m.r. (60 MHz; $CDCl_3$) δ/ppm;

1.40 (3 H, s, CH_3)
1.47 (3 H, s, CH_3)

3.93-4.23 (2 H, m, CH_2)
4.33 (1 H, m, $CHCH_2$)
9.57 (1 H, d, $CHCHO$)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

25.15 (q, CH_3)
26.25 (q, CH_3)
65.55 (t, CH_2)
79.87 (d, $CHCH_2$)
111.25 (s, $OCMe_2O$)
201.65 (d, $CHCHO$)

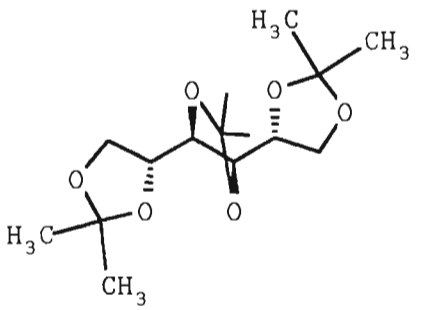
m/z (EI):

130(M^+, 0.2), 115(84.8), 101(100), 86(2.1), 85(34.8), 59(16.9) and 43(87.4).

5.2.4.2.2 DI-O-BENZYLGLYCERALDEHYDE.

1,2-3,4-5,6-Isopropylidene-(D)-mannitol **(118)**

(D)-Mannitol **(116)** (30 g, 164.68 mmol), in acetone (400ml) and *conc.* H_2SO_4 (3 ml), was stirred overnight at room temperature. After neutralisation with lead carbonate, the mixture was filtered and the filtrate evaporated under reduced pressure. Recrystallisation of the crude product afforded the triacetone mannitol (34.12 g, **69%**).



$C_{15}H_{26}O_6$ **MW** 302.37

m.p.: 68-70°C (from absolute EtOH) (Lit.,[119] 68-70°C).

$[\alpha]_D^{19.5}$: +12.2° (*c* 0.49, absolute EtOH) [Lit.,[119] $[\alpha]_D^{20}$ +12.5° (*c* 0.81, absolute EtOH)]

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.36 (6 H, s, 2 × CH_3)
1.39 (6 H, s, 2 × CH_3)
1.43 (6 H, s, 2 × CH_3)
3.93-3.96 (4 H, m, 2 × CH_2)
3.96-4.12 (2 H, m, H-3 and H-4)
4.15-4.21 (2 H, m, H-2 and H-5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

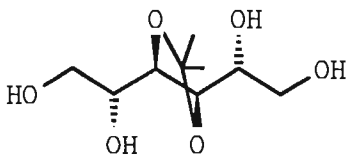
25.98 (q, CH_3)
27.17 (q, CH_3)
28.13 (q, CH_3)
66.92 (t, CH_2)
76.80 (d, C-3 and C-4)
80.06 (d, $CHCH_2$)
110.22 (s, $OCMe_2O$)
110.81 (s, OCO)

m/z (EI):

287(M^+-15, 18), 244(1), 229(1), 201(2), 143(93), 101(100), 85(36), 83(21), 73(24), 72(20) and 69(17).

3,4-Isopropylidene-(D)-mannitol **(119)**

Triacetone mannitol **(118)** (10.0 g, 33.11 mmol) was dissolved in a mixture of acetic acid-water (200 ml, 7:3). The solution was heated at 40°C (water bath) for 1.5 h. The solution was then rapidly vaporated under reduced pressure, at 40-50°C. The resulting residue was extracted with acetone. Removal of the acetone under reduced pressure afforded the crude product. Recrystallisation (from benzene) afforded the title compound (6.06 g, **83%**).



$C_9H_{18}O_6$ **MW** 222.24

m.p.: Not determined (Lit.,[118] 86-87°C)

$[\alpha]_D^{30}$: +25° (*c* 0.60, H_2O) [Lit., $[\alpha]_D$ +29° (*c* 1.0, H_2O)].

^{1}H n.m.r. (200 MHz; $CDCl_3/CD_3OD$) δ/ppm:

1.39 (6 H, s, 2 × CH_3)
3.64-3.71 (4 H, m, 2 × CH_2)
3.77-3.84 (2 H, m, H-3 and H-4)
3.93-3.96 (2 H, m, 2 × CHOH)
4.72 (4 H, broad s, 4 × OH)

^{13}C n.m.r. (50 MHz; $CDCl_3/CD_3OD$) δ/ppm:

27.14 (q, CH_3)
64.40 (t, CH_2)
73.94 (d, CHOH)
80.42 (d, C-3 and C-4)
110.39 (s, $OCMe_2O$)

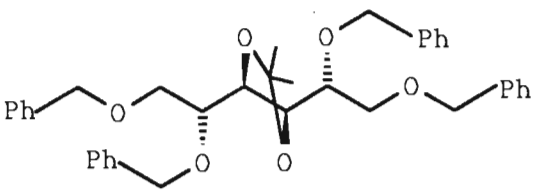
m/z (EI):

207(M^+-15, 31), 191(5), 161(24), 131(6), 129(16), 115(17), 103(75), 85(34), 60(6), 59(100), 57(12) and 43(11).

$C_9H_{18}O_6$ (222.24) Calculated: C 48.64 H 8.16
Found: C 48.73 H 8.34

1,2-5,6-Tetra-O-benzyl-3,4-O-isopropylidene-(D)-mannitol **(120)**

The tetrol **(119)** (1.0 g, 4.51 mmol) was treated with benzyl chloride (16.0 ml, 139.03 mmol) and potassium hydroxide (9.0 g, 160.40 mmol). The mixture was heated at 130-140°C for 2 h. After cooling to room temperature, water (30 ml) was added and the mixture was extracted with chloroform. The organic phase was washed with water, dried and concentrated under reduced pressure. The crude oil was purified by flash chromatography, using benzene-diethyl ether (40:1) as eluant, to afford the product (1.60 g, **61%**).



$C_{37}H_{42}O_6$ **MW** 582.74

$[\alpha]_D^{26}$: +13.21° (*c* 0.53, C_6H_6).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.35 (6 H, s, 2 × CH_3)
3.63 and 3.75 (4 H, ABX system, J_{BX} 6.8 Hz, 2 × CH_2CH)
3.75 (2 H, dd, *J* 11.1 and 3.1 Hz, 2 × $CHOCMe_2O$)
4.57 and 4.73 (4 H, AB system, J_{AB} 11.8 Hz, 2 × $CHOCH_2Ph$)

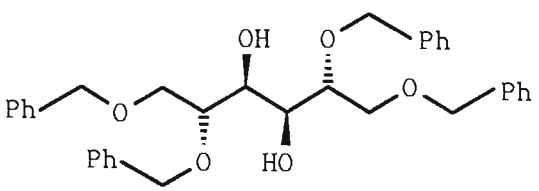
^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

27.21 (q, CH_3)
70.72 (t, CH_2CH)
72.94 (t, CH_2OCH_2Ph)
73.47 (t, $CHOCH_2Ph$)
78.66 (d, $CHOCMe_2O$)
79.39 (d, $CHOCH_2Ph$)
110.01 (s, CMe_2)
127.86, 127.93, 128.24, 128.59, 128.67 (d, *C*H aromatics)
138.56 (s, CCH_2 aromatic)
138.54 (s, CCH_2 aromatic)

$C_{37}H_{42}O_6$ (582.74) Calculated: C 76.26 H 7.27
Found: C 76.58 H 7.24

1,2-5,6-Tetra-O-benzyl-(D)-mannitol **(121)**

A mixture of the tetra-benzyl ether **(120)** (6.0 g, 10.31 mmol) in acetic acid-water (123 ml, 7:3) was heated at 100°C (water bath) for 1.5 h. Removal of the solvent under reduced pressure afforded an oil. Purification by flash chromatography, using hexane-ethyl acetate as eluant, afforded the diol (5.28 g, **95%**).



$C_{34}H_{38}O_6$ **MW** 542.68

$[\alpha]_D^{21.8}$: -13.12° (*c* 0.68, C_6H_6).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.07 (2 H, broad s, 2 × O*H*)
3.65-3.79 (6 H, m, 2 × C*H*$_2$OCH$_2$Ph and 2 × C*H*CH$_2$)
3.97 (2 H, m, 2 × C*H*OH)
4.54 (4 H, s, 2 × CHOC*H*$_2$Ph)
4.58 and 4.73 (4 H, AB system, J_{AB} 11.5 Hz, 2 × CHOC*H*$_2$Ph)
7.30 (20 H, H, 5 × C$_6$*H*$_5$)

^{13}C n.m.r (200 MHz; $CDCl_3$) δ/ppm:

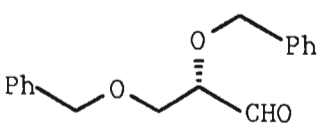
70.09 (d, *C*HOH)
70.37 (t, *C*H$_2$CH)
73.23 (t, CHO*C*H$_2$Ph)
73.69 (t, CHO*C*H$_2$Ph)
79.36 (d, *C*HCH$_2$)
128.02, 128.32, 128.76 (d, *C*H aromatics)

138.39 (s, CCH_2 aromatic)
138.55 (s, CCH_2 aromatic).

$C_{34}H_{38}O_6$ (542.68) Calculated: C 75.25 H 7.08
Found: C 75.12 H 7.05

(R)-2,3-Di-O-benzylglyceraldehyde **(115)**

A solution of the diol **(121)** (2.0 g, 3.69 mmol) in acetic acid (20 ml) was treated with lead tetraacetate (1.64 g, 3.69 mmol). The reaction mixture was vigorously stirred at room temperature. Small portions of oxidant [$Pb(OAc)_4$] were added until t.l.c. revealed disappearance of the alcohol **(121)**. After 1.5 h., the lead salts were removed by addition of 0.5 M oxalic acid solution (50 ml). The resulting precipitate was filtered off. The filtrate was dried and concentrated to a crude oil. Subsequent purification by flash chromatography, using hexane-ethyl acetate (93:7), afforded the aldehyde (1.21 g, **61%**).



$C_{17}H_{18}O_3$ **MW** 270.33

$[\alpha]_D^{28.0}$: +26.64° (*c* 1.31, C_6H_6) [Lit.,[121] $[\alpha]_D$ +52° (*c* 2.0, C_6H_6)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.73 (2 H, d, *J* 1.3 Hz, CH_2CH)
3.95 (1 H, m, $CHCH_2$)

4.48 and 4.54 (2 H, AB system, J_{AB} 12.2 Hz, CH_2OCH_2Ph)
4.64 and 4.71 (2 H, AB system, J_{AB} 12.0 Hz, $CHOCH_2Ph$)
7.31 (10 H, m, 2 × C_6H_5)
9.68 (1 H, d, *J* 1.1 Hz, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

69.23 (t, CH_2CH)
72.82 (t, CH_2OCH_2Ph)
73.71 (t, $CHOCH_2Ph$)
82.87 (d, $CHCH_2$)
128.02, 128.12, 128.35 (d, CH aromatics)
128.40, 128.75, 128.85 (d, CH aromatics)
137.93 (s, CCH_2 aromatic)
137.55 (s, CCH_2 aromatic)

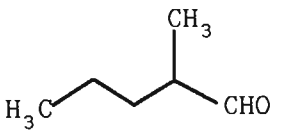
m/z (EI):

121(M^+-129, 0.3), 120(3.1), 107(2.6), 91(100), 77(2.6), 65(10.4), 43(0.2) and 44(0.8).

5.2.5 THE α-ALKYL ALDEHYDE.

(±)-2-Methylpentanal **(122)**

Was commercially[122] available.



$C_6H_{12}O$ **MW** 100.16

b.p.: Not determined (Lit.,[122] 118°C).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm;

0.93 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.02 (3 H, d, *J* 7.0 Hz, CH_3CH)
1.29-1.47 (4 H, m, CH_2CH_2)
1.69 (1 H, m, $CHCH_3$)
9.62 (1 H, d, *J* 2.0 Hz, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

13.28 (q, CH_3CH_2)
14.07 (q, CH_3CH)
20.15 (t, CH_2CH_3)
32.66 (t, CH_2CH)
46.13 (d, $CHCH_3$)
205.52 (d, CHCHO)

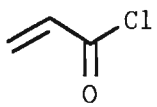
m/z (EI):

100(M^+, 9), 71(17), 58(100), 57(17), 43(48) and 29(70).

5.2.6 THE ACTIVATED VINYL SYSTEMS.

Acryloyl chloride

Acrylic acid (68.6 ml, 1000.54 mmol) and PCl_3 (29.1 ml, 333.53 mmol) was gently heated to reflux, with the internal temperature maintained at 60-70°C by cooling, for 15 min. The mixture was then stirred at room temperature for 2 h. After separation of the mixture into two layers, the organic layer was distilled over a catalytic amount of hydroquinone to afford the title compound (51.0 g, **56%**).



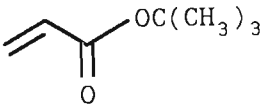
C_3ClH_3O **MW** 90.51

b.p.: 69-72°C/atmospheric pressure (Lit.,[208] 72-76°C)

5.2.6.1 *tert*-BUTYL ACRYLATE.

tert-Butyl acrylate **(86 C)**

tert-Butyl alcohol (29.0 g, 391.26 mmol), *N*,*N*-dimethyl-aniline (29.2 ml, 230 mmol), acryloyl chloride (18.7 ml, 230 mmol) and hydroquinone (0.5 g, 4.54 mmol), were refluxed in anhydrous diethyl ether for 7 d. The liquid was decanted from the white solid, washed with 2 N hydrochloric acid (2 × 40 ml), 1 N sodium hydroxide (40 ml), dried and concentrated under reduced pressure. Distillation of the crude product, (over hydroquinone), afforded the title compound (5.80 g, **30%**).



$C_7H_{12}O_2$ **MW** 128.17

b.p.: 94-95°C/atmospheric pressure (Lit.,[209] 61-63°C/60 mm Hg)

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.49 (9 H, s, 3 × CH_3)
5.62-6.45 (3 H, m, CH_2 and CH)

m/z (EI):

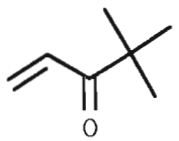
128(M^+, 0.1), 113(23.5), 73(14.3), 57(70.8) and 55(100).

5.2.6.2 *tert*-BUTYL VINYL KETONE.

tert-Butyl vinyl ketone **(86 D)**

Paraformaldehyde (4.50 g), *N*-methylanilinium trifluoroacetate (TAMA) (11.06 g, 50.00 mmol) and 3,3-dimethylbutan-2-one (pinacolone) (6.25 ml, 50.00 mmol), in THF (50 ml), was refluxed overnight. The mixture was cooled and a further amount of paraformaldehyde (2.25 g), TAMA (5.53 g, 25.00 mmol) and THF (25 ml) was added. Reflux was continued, (at least 31 h. in total), and the mixture was diluted with pentane and water. The organic layer was extracted with pentane. The combined organic layer was washed water, half-saturated aqueous sodium hydrogen carbonate and dried.

Concentration under reduced pressure, followed by flash chromatography, afforded the pure vinyl ketone.



$C_7H_{12}O$ **MW** 112.17

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.17 (9 H, s, 3 × CH_3)
5.57-6.88 (3 H, m, CH_2 and CH)

5.2.7. THE COUPLED α-(ALKOXY/ALKYL)-SUBSTITUTED ALDEHYDE-ACRYLIC SYSTEMS.

GENERAL PROCEDURE 4:

Reactions of the α-alkoxy/methyl/amino aldehydes with the activated vinyl systems.

The aldehyde (1 equivalent) was added, (neat), to a stirred mixture of the vinyl component (1.1/4.0 equivalents) and catalyst (0.1-1.0 equivalents) at ambient temperature; in those cases where 1 equivalent of catalyst was employed, a four-fold excess of vinyl component was used. The reactions were stoppered and stirred at room temperature until ^{1}H n.m.r. spectroscopy indicated consumption of the aldehyde signal. The reaction mixture was diluted with dichloro-

methane, (or chloroform), and sequentially washed with dilute hydrochloric acid (2 N) and water. The organic layer was dried and concentrated under reduced pressure to afford the crude product. Ratio analysis, (see TABLE 5/25), was carried out directly on the diastereomeric mixture, before and/or after isolation by flash chromatography.

However, for the *N*,*N*-dibenzylated products, viz., **(193)** and **(216)**, workup consisted of direct flash chromatography.

In some cases, further chromatography afforded the separated diastereomers.

5.2.7.1 THE TAI DERIVATIVES.

GENERAL PROCEDURE 5:

Determination of diastereomeric ratios/stereosubstructure by TAI derivatisation.

An ^{1}H n.m.r. sample, (crude and/or purified), of the diastereomeric mixture [(±) 15-30 mg] was treated with an excess (5-10%, or 10-20% for the *tertiary amino* adducts) of trichloroacetylisocyanate (TAI) **(125)**. The sample tube was shaken to ensure mixing and was given a short time, (about 5-10 min.), to ensure complete reaction. Simple integration (or analysis) of the carbamate N*H* signals (8.5-10 ppm) then provided the diastereomeric ratio and allowed direct assignment of stereosubstructure.

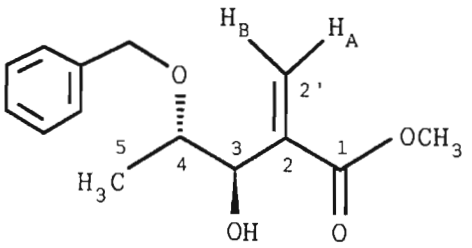
5.2.7.2. THE α-METHYLENE-β-HYDROXY-γ-ALKOXY/METHYL ESTERS AND KETONES.

Methyl 4-(benzyloxy)-3-hydroxy-2-methylenepentanoate **(130)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(11)** (1.521 g, 9.26 mmol), methyl acrylate (0.92 ml, 10.19 mmol) and DABCO **(56)** (0.104 g, 0.93 mmol), using hexane-acetone (80:20) as eluant, furnished the pure diastereomeric mixture (1.577 g, **68%**). The diastereomers were separated by preparative t.l.c. using hexane-ethyl acetate (93:7) as eluant.

$C_{14}H_{18}O_4$ **MW** 250.30

Major isomer: *anti* **(130 A)**



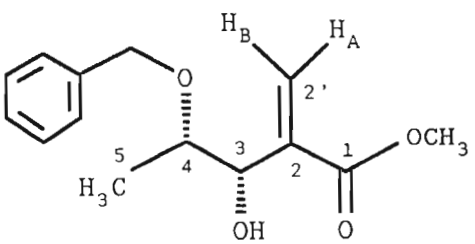
^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:
1.07 (d, 3 H, *J* 6.4 Hz, H-5)
3.08 (1 H, broad s, O*H*)
3.67 (3 H,s, C*H*$_3$O)
3.78 (1 H, dq, *J* 6.4 and 3.8 Hz, H-5)
4.56 (2 H, s, C*H*$_2$O)
4.70 (1 H, m, H-3)
5.98 (1 H, t, *J* 1.5 Hz, H_B)
6.31 (1 H, dd, *J* 1.5 and 1.2 Hz, H_A)
7.26 (5 H, m, C$_6$*H*$_5$)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

13.43 (q, C-5)
51.71 (q, CH_3O)
70.81 (t, CH_2O)
71.83 (d, C-3)
76.16 (d, C-4)
126.59, 127.58, 127.70 (d, CH aromatics)
128.31 (t, C-2')
138.36 (s, CCH_2 aromatic)
139.19 (s, C-2)
166.57 (s, C-1)

$C_{14}H_{18}O_4$ (250.30) Calculated: C 67.18 H 7.25
Found: C 67.19 H 7.11

Minor isomer: *syn* **(130 B)**



^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.24 (3 H, d, *J* 6.3 Hz, H-5)
2.93 (1 H, broad s, O*H*)
3.68 (3 H, s, CH_3O)
3.73 (1 H, m, H-4)
4.39 and 4.61 (2 H, AB system, J_{AB} 11.7 Hz, CH_2O)
4.48 (1 H, m, H-3)

5.91 (1 H, t, *J* 1.3 Hz, H_B)
6.30 (1 H, dd, *J* 1.3 and 0.5 Hz, H_A)
7.28 (5 H, m, C_6H_5)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

16.23 (q, C-5)
51.78 (q, CH_3O)
71.34 (t, CH_2O)
73.81 (d, C-3)
77.16 (d, C-4)
126.57, 126.67, 127.77 (d, CH aromatics)
128.34 (t, C-2')
138.24 (s, CCH_2 aromatic)
140.51 (s, C-2)
166.76 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.133

m/z (EI):

174(M^+-77, 6), 116(3), 91(100), 77(3) and 65(6)

$C_{14}H_{18}O_4$ (250.30) Calculated: C 67.18 H 7.25
Found: C 66.96 H 6.91

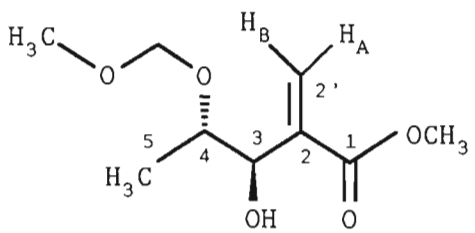
(3R, 4S) and (3S, 4S)-Methyl 3-hydroxy-4-(methoxymethoxy)-2-methylenepentanoate **(131)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(104)** (1.02g, 8.64 mmol), methyl acrylate (0.86 ml, 9.50 mmol) and (±)-3-quinuclidinol **(71)** (0.109 g, 0.86 mmol), using

hexane-ethyl acetate (85:15) as eluant, furnished the pure diastereomeric mixture (1.058 g, **60%**). The diastereomers were separated using hexane-ethyl acetate (93:7) as eluant.

$C_9H_{16}O_5$ **MW** 204.23

Major isomer: *anti* **(131 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.10 (3 H, d, *J* 6.5 Hz, H-5)
2.98 (1 H, d, *J* 4.6 Hz, O*H*)
3.39 (3 H, s, CH_3OCH_2)
3.78 (3 H, s, CH_3OCO)
4.00 (1 H, dq, *J* 6.5 and 4.0 Hz, H-4)
4.63 (1 H, m, H-3)
4.70 (2 H, s, OCH_2O)
6.03 (1 H, t, *J* 1.5 Hz, H_B)
6.37 (1 H, t, *J* 1.3 Hz, H_A)

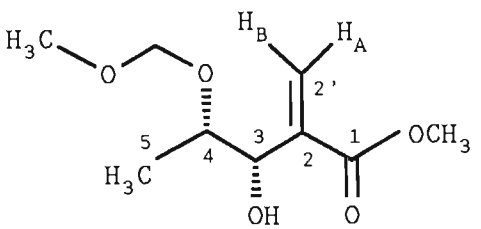
^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.01 (q, C-5)
52.08 (q, CH_3OCO)
55.70 (q, CH_3OCH_2)
73.19 (d, C-3)
74.83 (d, C-4)
95.45 (t, OCH_2O)

127.37 (t, C-2')
139.25 (s, C-2)
167.11 (s, C-1)

$C_9H_{16}O_5$ (204.23) Calculated: C 52.93 H 7.90
Found: C 52.93 H 7.93

Minor isomer: *syn* **(131 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm;

1.18 (3 H, d, *J* 6.4 Hz, H-5)
3.18 (1 H, broad s, O*H*)
3.34 (3 H, s, CH_3OCH_2)
3.76 (3 H, s, CH_3OCO)
3.85 (1 H, dq, *J* 6.4 and 4.9 Hz, $CHCH_3$)
4.36 (1 H, m, H-3)
4.60 and 4.67 (2 H, AB system, J_{AB} 6.9 Hz, OCH_2O)
5.92 (1 H, t, *J* 1.3 Hz, H_B)
6.32 (1 H, t, *J* 0.6 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.43 (q, C-5)
52.10 (q, CH_3OCO)
55.77 (q, CH_3OCH_2)

74.42 (d, C-3)
76.68 (d, C-4)
96.17 (t, OCH_2O)
127.19 (t, C-2')
140.83 (s, C-2)
167.18 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm;

Δ (NH_{syn} - NH_{anti}) = 0.129

$C_9H_{16}O_5$ (204.23) Calculated: C 52.93 H 7.90
Found: C 52.67 H 8.10

m/z (EI):

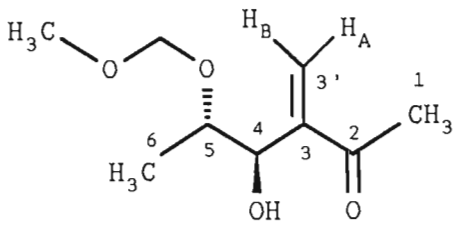
173(M^+-31, 2), 160(1), 145(1), 143(4), 142(9), 129(7), 128(19), 115(100), 89(16), 83(61), 57(8) and 55(17).

(4R, 5S) and (4S, 5S)-4-Hydroxy-5-(methoxymethoxy)-3-methylenehexan-2-one **(132)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(104)** (1.59 g, 13.46 mmol), methyl vinyl ketone (1.23 ml, 14.81 mmol) and (±)-3-quinuclidinol **(71)** (0.172 g, 1.35 mmol), using hexane-ethyl acetate (85:15) as eluant, furnished the diastereomeric mixture (1.300 g, **80%**). Further separation by preparative t.l.c., using hexane-ethyl acetate (93:7) as eluant, afforded the major (*anti*) diastereomer.

$C_9H_{16}O_4$ MW 188.23

Major isomer: *anti* **(132 A)**



^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.04 (3 H, d, *J* 6.5 Hz, H-6)
2.35 (3 H, s, H-1)
3.00 (1 H, broad s, O*H*)
3.37 (3 H, s, CH_3OCH_2)
3.92 (1 H, dq, *J* 6.5 and 3.8 Hz, H-5)
4.68 (1 H, m, H-4)
4.69 (s, 2 H, CH_2O)
6.19 (1 H, dd, *J* 1.4 and 0.5 Hz, H_B)
6.23 (1 H, t, *J* 0.6 Hz, H_A)

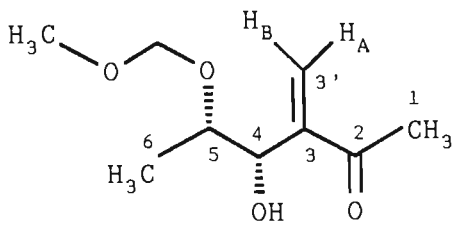
^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:
13.66 (q, C-6)
25.94 (q, C-1)
55.09 (q, CH_3OCH_2)
71.60 (d, C-4)
74.50 (d, C-5)
94.86 (t, CH_2O)
126.87 (t, C-3')
147.39 (s, C-3)
199.39 (s, C-2)

m/z (EI):

171(M^+-17, 0.4), 170(3.5), 169(32.8), 127(35.8), 153(10.6), 45(98.2) and 43(100).

$C_9H_{16}O_4$ (188.23) Calculated: C 57.43 H 8.57
Found: C 57.45 H 8.39

Minor isomer: *syn* **(132 B)**



^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm: (selected shifts)

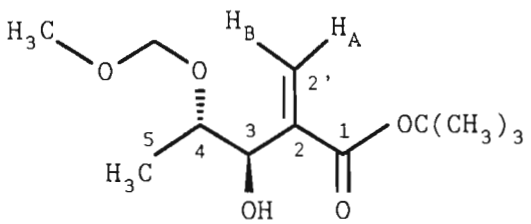
1.16 (3 H, d, *J* 6.4 Hz, H-6)
1.72 (1 H, broad d, *J* 1.0 Hz, O*H*)
2.36 (3 H, s, C-1)
3.35 (3 H, s, CH_3OCH_2)
4.65 (2 H, s, CH_2O)
6.13 (1 H, d, *J* 1.2 Hz, H_B)

(3R, 4S) and (3S, 4S)-tert-Butyl 3-hydroxy-4-(methoxymethoxy)-2-methylenepentanoate **(133)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(104)** (0.296 g, 2.51 mmol), *tert*-butyl acrylate **(86 C)** (0.354 g, 2.76 mmol) and (±)-3-quinuclidinol **(71)** (0.032 g, 0.25 mmol), using hexane-ethyl acetate (65:35) as eluant, furnished the pure diastereomeric mixture (0.241 g, **39%**).

$C_{12}H_{22}O_5$ **MW** 246.31

Major isomer: *anti* **(133 A)**



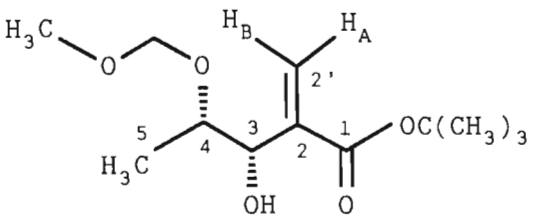
^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.10 (3 H, d, *J* 6.4 Hz, H-5)
1.50 (9 H, s, $[CH_3]_3C$)
3.03 (1 H, broad s, O*H*)
3.37 (3 H, s, CH_3O)
3.98 (1 H, dq, *J* 6.4 and 4.1 Hz, H-4)
4.56 (1 H, m, H-3)
4.68 (2 H, s, CH_2O)
5.86 (1 H, t, *J* 1.6 Hz, H_B)
6.25 (1 H, dd, *J* 1.7 and 1.0 Hz, H_A)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

14.16 (q, C-5)
28.08 (q, $[CH_3]_3C$)
55.51 (q, CH_3O)
73.18 (d, C-3)
74.70 (d, C-4)
81.28 (s, $C[CH_3]_3$)
95.13 (t, CH_2O)
125.86 (t, C-2')
140.67 (s, C-2)
165.50 (s, C-1)

Minor isomer: *syn* **(133 B)**



^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm: (selected shifts)

1.19 (3 H, d, *J* 6.4 Hz, H-5)
1.52 (9 H, s, $[CH_3]_3C$)
3.35 (3 H, s, CH_3O)
3.83 (1 H, m, H-4)
4.66 (2 H, s, CH_2O)
5.82 (1 H, d, *J* 1.5 Hz, H_B)
6.23 (1 H, d, *J* 0.7 Hz, H_A)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

17.32 (q, C-5)
28.08 (q, $[CH_3]_3C$)
55.51 (q, CH_3O)
74.27 (d, C-3)
76.47 (d, C-4)
81.20 (s, $C[CH_3]_3$)
95.84 (t, CH_2O)
125.50 (t, C-2)
142.14 (s, C-2)
165.50 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.098

m/z (EI):

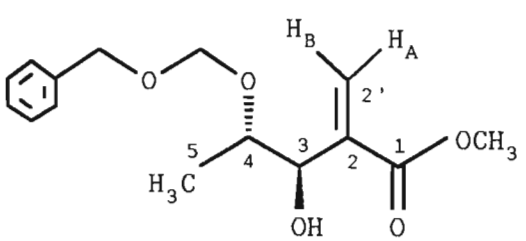
173(M^+-73, 4), 158(1), 145(3), 130(1), 129(12), 128(26), 115(14), 114(65), 111(23), 113(5), 102(4), 97(4), 96(12), 83(24), 57(73), 55(9) and 45(100).

$C_{12}H_{22}O_5$ (246.31) Calculated: C 58.52 H 9.01
Found (mixture): C 58.64 H 8.81

Methyl 4-[(benzyloxy)methoxy]-3-hydroxy-2-methylenepentanoate **(134)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(105)** (2.91 g, 14.98 mmol), methyl acrylate (5.40 ml, 59.92 mmol) and DABCO **(56)** (1.681 g, 14.98 mmol), using hexane-ethyl acetate (80:20) as eluant, furnished the pure diastereomeric mixture (1.722 g, **41%**). Further separation using hexane-ethyl acetate (90:10) eluant, afforded the pure major (*anti*) diastereomer.

Major isomer: *anti* **(134 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

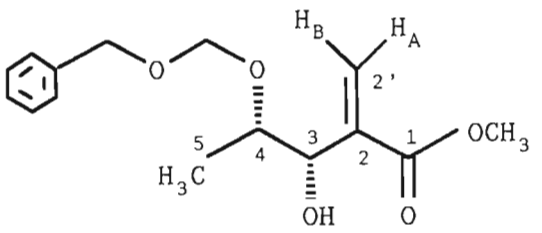
1.11 (3 H, d, *J* 6.4 Hz, H-5)

3.14 (1 H, broad s, O*H*)
3.72 (3 H, s, CH_3O)
4.07 (1 H, dq, *J* 6.4 and 4.0 Hz, H-4)
4.59 and 4.65 (2 H, AB system, J_{AB} 11.7 Hz, CH_2Ph)
4.66 (1 H, m, H-3)
4.81 (2 H, s, OCH_2O)
5.99 (1 H, t, *J* 1.5 Hz, H_B)
6.36 (1 H, dd, *J* 1.3 and 0.7 Hz, H_B)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.83 (q, C-5)
51.88 (q, CH_3O)
69.56 (t, CH_2Ph)
72.90 (d, C-3)
74.56 (d, C-4)
99.99 (t, OCH_2O)
126.98 (t, C-2')
127.72, 127.85, 128.41 (d, CH aromatics)
137.64 (s, CCH_2 aromatic)
138.98 (s, C-2)
166.55 (s, C-1)

Minor isomer: *syn* **(134 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.23 (3 H, d, *J* 6.4 Hz, H-5)
3.00 (1 H, broad s, O*H*)
3.73 (3 H, s, CH_3O)
3.96 (1 H, dq, *J* 6.3 and 4.7 Hz, H-4)
4.42 (1 H, m, H-3)
4.55 and 4.63 (2 H, AB system, J_{AB} 11.7 Hz, CH_2Ph)
4.82 (2 H, s, OCH_2O)
5.99 (1 H, t, *J* 1.2 Hz, H_B)
6.36 (1 H, t, *J* 1.4 Hz, H_A)
7.30 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.28 (q, C-5)
51.91 (q, CH_3O)
69.67 (t, CH_2Ph)
74.11 (d, C-3)
76.16 (d, C-4)
93.69 (t, OCH_2O)
126.79 (t, C-2')
127.77, 127.84, 128.43 (d, CH aromatics)
137.47 (s, CCH_2 aromatic)
140.39 (s, C-2)
166.61 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.030

m/z (EI):

203(M^+-77, 0.1), 173(0.6), 158(0.1), 129(3.6), 115(29.6), 91(100), 77(4.9), 65(12.1) and 59(1.5)

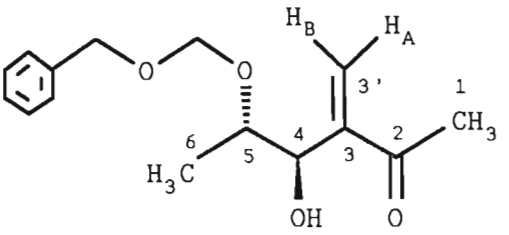
$C_{15}H_{20}O_5$ (280.32) Calculated: C 64.27 H 7.19
Found (mixture): C 64.19 H 7.02

5-[(Benzyloxy)methoxy]-4-hydroxy-3-methylenehexan-2-one **(135)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(105)** (0.120 g, 0.62 mmol), methyl vinyl ketone (0.06 ml, 0.68 mmol) and (±)-3-quinuclidinol **(71)** (0.008 g, 0.06 mmol), using hexane-ethyl acetate (70:30) as eluant, furnished the major (*anti*) diastereomer and the pure diastereomeric mixture (0.129 g, **79%**).

$C_{15}H_{20}O_4$ **MW** 264.32

Major isomer: *anti* **(135 A)**



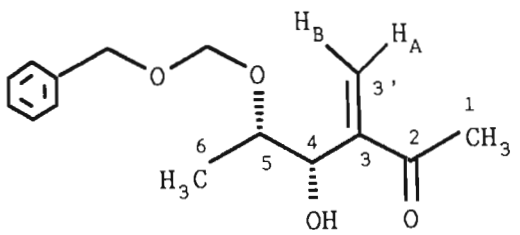
^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

1.06 (3 H, d, *J* 6.4 Hz, H-6)
2.32 (3 H, s, H-1)
2.97 (1 H, broad s, O*H*)
4.02 (1 H, dq, *J* 6.4 and 3.9 Hz, H-5)
4.62 (2 H, s, CH_2Ph)
4.68 (1 H, m, H-4)
4.82 (1 H, s, OCH_2O)
6.17 (1 H, t, *J* 0.7 Hz, H_B)
6.19 (1 H, t, *J* 0.72 Hz, H_A)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

14.00 (q, C-6)
26.23 (q, C-1)
69.67 (t, CH_2Ph)
72.37 (d, C-4)
74.84 (d, C-5)
93.28 (t, OCH_2O)
127.30 (t, C-3')
127.71, 127.85, 128.43 (d, *C*H aromatics)
137.75 (s, CCH_2 aromatic)
147.14 (s, C-3)
199.62 (s, C-2)

Minor isomer: *syn* **(135 B)**



^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm: (selected shifts)

1.18 (3 H, d, *J* 6.4 Hz, H-6)
2.30 (3 H, s, H-1)
4.59 (2 H, s, CH_2Ph)
4.82 (2 H, s, OCH_2O)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm:

17.18 (q, C-6)
26.20 (q, C-1)
69.51 (t, CH_2Ph)
72.71 (d, C-4)
76.35 (d, C-5)
93.68 (t, OCH_2O)
126.86 (t, C-3')
127.77, 127.92, 128.53 (d, CH aromatics)
137.68 (s, CCH_2 aromatic)
147.24 (s, C-3)
199.57 (s, C-2)

m/z (EI):

173(M^+-91, 0.2), 158(1.4), 140(3.8), 130(0.4), 115(0.4), 114(5.1), 100(2.9), 99(47.7), 91(100), 89(2.8), 77(2.9), 65(9.9), 58(1.2) and 43(24.4).

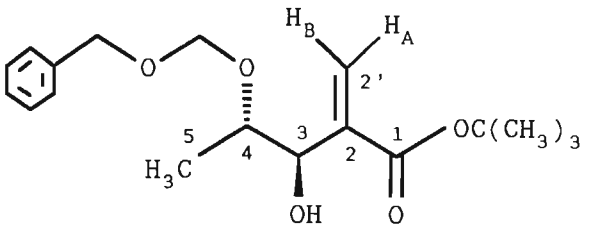
$C_{15}H_{20}O_4$ (264.32) Calculated: C 68.16 H 7.63
Found (mixture): C 67.94 H 7.42

(3R, 4S) and (3S, 4S)-tert-Butyl-4-[(benzyloxy)methoxy]--3-hydroxy-2-methylenepentanoate **(64)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(105)** (0.194 g, 1.00 mmol), *tert*-butyl acrylate **(86 C)** (0.141 g, 1.10 mmol) and (±)-3-quinuclidinol **(71)** (0.013 g, 0.10 mmol), using hexane-ethyl acetate (93:7) as eluant, furnished the major (*anti*) diastereomer and the pure diastereomeric mixture (0.097 g, **30%**).

$C_{18}H_{26}O_5$ **MW** 322.41

Major isomer: *anti* **(64 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

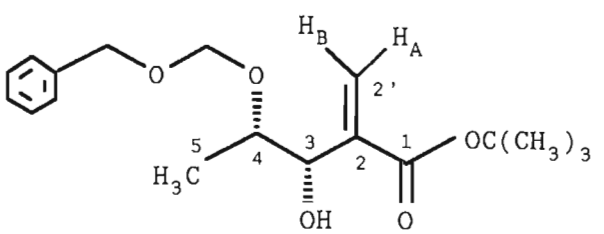
1.13 (3 H, d, *J* 6.4 Hz, H-5)
1.48 (9 H, s, $[CH_3]_3C$)
3.38 (1 H, d, *J* 4.9 Hz, O*H*)
4.07 (1 H, dq, *J* 6.4 and 4.1 Hz, H-4)
4.59 (1 H, m, H-3)
4.63 (2 H, s, CH_2Ph)
4.82 (2 H, s, OCH_2O)

5.88 (1 H, t, *J* 1.6 Hz, H_B)
6.27 (1 H, dd, *J* 1.5 and 1.0 Hz, H_A)
7.32 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.19 (q, C-5)
28.03 (q, $[CH_3]_3C$)
69.56 (t, CH_2Ph)
73.25 (d, C-3)
74.83 (d, C-4)
81.37 (s, $C[CH_3]_3$)
93.09 (t, OCH_2O)
126.03 (t, C-2')
127.72, 127.87, 128.42 (d, *C*H aromatics)
137.66 (s, CCH_2O aromatic)
140.25 (s, C-2)
165.45 (s, C-1)

Minor isomer: *syn* **(64 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.23 (3 H, d, *J* 6.4 Hz, H-5)
1.45 (9 H, s, $[CH_3]_3C$)
2.85 (1 H, broad s, O*H*)

3.92 (1 H, dq, *J* 6.4 and 4.9 Hz, H-4)
4.38 (1 H, m, H-3)
4.61 (2 H, s, CH_2Ph)
4.81 (2 H, s, OCH_2O)
5.85 (1 H, t, *J* 1.3 Hz, H_B)
6.26 (1 H, dd, *J* 1.5 and 0.8 Hz, H_A)
7.32 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.36 (q, C-5)
28.03 (q, $[CH_3]_3C$)
69.65 (t, CH_2Ph)
74.31 (d, C-3)
76.63 (d, C-4)
81.28 (s, $C[CH_3]_3$)
93.76 (t, OCH_2O)
125.73 (t, C-2')
127.77, 127.87, 28.41 (d, CH aromatics)
137.67 (s, CCH_2O aromatic)
141.88 (s, C-2)
165.46 (s, C-1)

m/z (EI):

249(M^+-73, 0.1), 248(0.5), 221(0.6), 204(3.8), 158(0.4), 115(7.4), 101(29.3), 92(36.8), 91(100), 77(1.5) and 65(6).

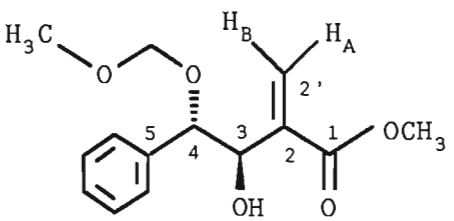
$C_{18}H_{26}O_5$ (322.41) Calculated: C 67.06 H 8.13
Found (mixture): C 67.06 H 7.94

Methyl 3-Hydroxy-4-(methoxymethoxy)-2-methylene-5-phenyl-butanoate **(136)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(106)** 0.650 g, 3.61 mmol), methyl acrylate (0.36 ml, 3.97 mmol) and DABCO **(56)** (0.040 g, 0.36 mmol), using hexane-ethyl acetate (85:15) as eluant, furnished the pure diastereomeric mixture (0.394 g, **41%**). The diastereomers were separated using hexane-ethyl acetate (95:5)as eluant.

$C_{14}H_{18}O_5$ **MW** 266.30

Minor isomer: *anti* **(136 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

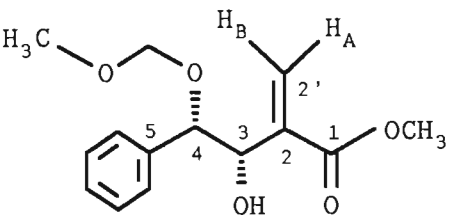
2.96 (1 H, broad s, O*H*)
3.32 (3 H, s, CH_3OCH_2)
3.75 (3 H, s,$COOCH_3$)
4.52 and 4.56 (2 H, AB system, *J* 6.6 Hz, OCH_2O)
4.77 (1 H, d, *J* 5.24 Hz, H-4)
4.82 (1 H, d, *J* 5.24 Hz, H-3)
5.67 (1 H, t, *J* 1.1 Hz, H_B)
6.23 (1 H, d, *J* 0.8 Hz, H_A)
7.29 (5 H, m, C_6H_5)

^{13}C n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

51.90 (q, $COOCH_3$)
55.64 (q, CH_3OCH_2)
74.04 (d, C-3)

79.83 (d, C-4)
94.33 (t, OCH_2O)
127.25 (t, C-2')
128.04, 128.10, 128.14 (d, CH aromatics)
137.23 (s, C-5 aromatic)
138.95 (s, C-2)
166.86 (s, C-1)

Major isomer: *syn* **(136 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.20 (1 H, broad s, O*H*)
3.33 (3 H, s, CH_3OCH_2)
3.60 (3 H, s, $COOCH_3$)
4.58 (2 H, s, OCH_2O)
4.67 (1 H, d, *J* 5.5 Hz, H-4)
4.78 (1 H, d, *J* 5.5 Hz, H-3)
5.91 (3 H, t, *J* 1.2 Hz, H_B)
6.27 (1 H, dd, *J* 1.1 and 0.6 Hz, H_A)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

51.74 (q, CH_3OCH_2)
55.85 (q, CH_3OCO)
74.59 (d, C-3)

80.71 (d, C-4)
94.75 (t, OCH_2O)
127.14 (t, C-2')
127.50, 128.08, 128.28 (d, CH aromatics)
138.08 (s, C-5 aromatic)
139.57 (s, C-2)
166.40 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.131

m/z (EI):

235(M^+-31, 0.1), 205(4.0), 189(0.2), 173(14.2), 151(100), 112(2.5), 106(6.0), 105(39.2), 99(7.1), 77(23.6), 65(4.4), 59(2.5), and 45(48.4).

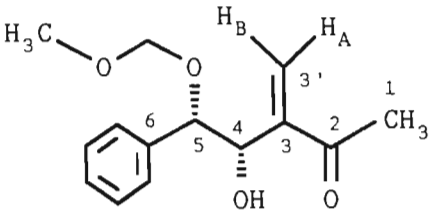
$C_{14}H_{18}O_5$ (266.30) Calculated: C 63.15 H 6.81
Found (mixture): C 63.25 H 6.43

4-Hydroxy-5-(methoxymethoxy)-3-methylene-5-phenylpentan-2-one **(137)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(106)** (0.295 g, 1.64 mmol), methyl vinyl ketone (0.15 ml, 1.80 mmol) and DABCO **(56)** (0.018 g, 0.16 mmol), using hexane-ethyl acetate (80:20) as eluant, furnished the major (*syn*) diastereomer (0.287 g, **70%**).

$C_{14}H_{18}O_4$ **MW** 250.30

Major isomer: *syn* **(137 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.32 (3 H, s, H-1)
3.16 (1 H, broad s, O*H*)
3.34 (3 H, s, CH_3OCH_2)
4.54 and 4.59 (2 H, AB system, *J* 6.6 Hz, OCH_2O)
4.79 (1 H, d, *J* 5.2 Hz, H-5)
4.86 (1 H, d, *J* 5.3 Hz, H-4)
5.80 (1 H, dd, *J* 1.2 and 0.4 Hz, H_B)
6.06 (1 H, t, *J* 0.5 Hz, H_A)
7.27 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

26.33 (q, CH_3OCH_2)
55.70 (q, C-1)
73.58 (d, C-4)
79.60 (d, C-5)
94.40 (t, OCH_2O)
127.60 (t, C-3')
127.99, 128.05, 128.11 (d, C*H* aromatics)
137.25 (s, C-6 aromatic)
146.65 (s, C-3)
199.95 (s, C-2)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.102

m/z (EI):

219(M^+-31, 0.1), 205(0.2), 128(5.8), 112(18.6), 151(100), 99(66), 77(27.1), 65(0.6), 45(60.9) and 43(23.8).

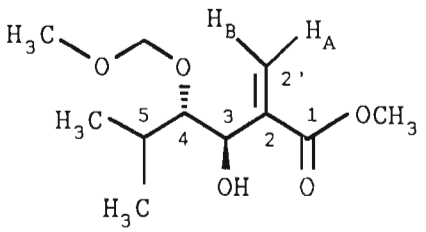
$C_{14}H_{18}O_4$ (250.30) Calculated: C 67.18 H 7.25
Found: C 67.25 H 7.27

Methyl 3-hydroxy-4-(methoxymethoxy)-5-methyl-2-methylene-hexanoate **(138)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(107)** (3.74 g, 25.59 mmol), methyl acrylate (9.22 ml, 102.36 mmol) and DABCO **(56)** (2.871 g, 25.59 mmol), using hexane-ethyl acetate (85:15) as eluant, furnished the pure diastereomeric mixture (1.426 g, **24%**).

$C_{11}H_{20}O_5$ **MW** 232.28

Major isomer: *anti* **(138 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

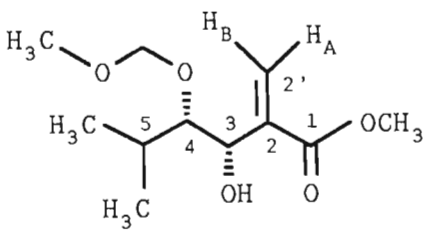
0.89-0.98 (6 H, d, $[CH_3]_2CH$)
1.86 (1 H, m, H-5)
3.10 (1 H, broad s, O*H*)

3.32 (3 H, s, CH_3OCH_2)
3.46 (1 H, dd, *J* 5.4 and 3.6 Hz, H-4)
3.73 (3 H, s, CH_3OCO)
4.50 (1 H, m, H-3)
4.56 (2 H, s, OCH_2O)
5.90 (1 H, t, *J* 1.4 Hz, H_B)
6.28 (1 H, t, *J* 1.4 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.68 (q, CH_3CH)
19.50 (q, CH_3CH)
30.40 (d, C-5)
51.83 (q, CH_3OCO)
56.12 (q, CH_3OCH_2)
70.72 (C-3)
86.24 (d, C-4)
98.31 (t, OCH_2O)
126.35 (t, C-2')
141.43 (s, C-2)
166.54 (s, C-1)

Minor isomer: *syn* **(138 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.89-0.98 (6 H, d, $[CH_3]_2CH$)
1.86 (1 H, m, H-5)
3.32 (3 H, s, CH_3OCH_2)
3.74 (3 H, s, CH_3OCO)
3.50 (1 H, dd, *J* 5.6 and 4.5 Hz, H-4)
4.55 and 4.60 (2 H, AB system, J_{AB} 6.6 Hz, OCH_2O)
4.47 (1 H, m, H-3)
5.92 (1 H, t, *J* 1.3 Hz, H_B)
6.29 (1 H, t, *J* 1.1 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.12 (q, CH_3CH)
20.23 (q, CH_3CH)
29.25 (d, C-5)
51.93 (q, CH_3OCO)
56.12 (q, CH_3OCH_2)
72.14 (d, C-3)
86.27 (d, C-4)
98.13 (t, OCH_2O)
127.36 (t, C-2')
139.62 (s, C-2)
167.24 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.125

m/z (EI):

201(M^+-31, 0.2), 170(0.1), 160(2.6), 142(4.9), 128(14.8), 127(7.4), 117(11.3), 115(100), 85(3.9) and 45(7.5).

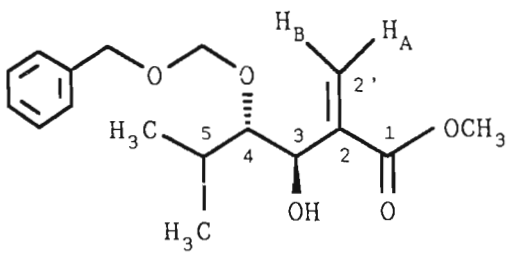
$C_{11}H_{20}O_5$ (232.28) Calculated: C 56.88 H 8.68
Found (mixture): C 56.33 H 9.23

Methyl 4-[(benzyloxy)methoxy]-3-hydroxy-5-methyl-2-methylenehexanoate **(139)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(108)** (1.145 g, 5.15 mmol), methyl acrylate (1.86 ml, 20.60 mmol) and DABCO **(56)** (0.578 g, 5.15 mmol), using hexane-ethyl acetate (95:5) as eluant, furnished the pure diastereomeric mixture (1.080 g, **68%**).

$C_{17}H_{24}O_5$ **MW** 308.38

Minor isomer: *anti* **(139 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

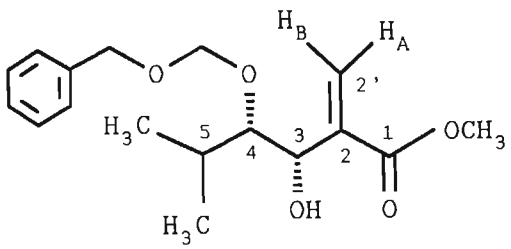
0.95-1.01 (6 H, d, $[CH_3]_2CH$)
1.93 (1 H, m, H-5)
3.01 (1 H, broad s, O*H*)
3.64 (1 H, dd, *J* 6.0 and 4,8 Hz, H-4)
3.72 (3 H, s, CH_3OCO)
4.59 (1 H, m, H-3)
4.62 (2 H, s, OCH_2Ph)
4.71 and 4.80 (2 H, AB system, J_{AB} 6.8 Hz, OCH_2O)
5.97 (1 H, t, *J* 1.3 Hz, H_B)
6.32 (1 H, t, *J* 0.8 Hz, H_A)
7.29 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.16 (q, CH_3CH)
20.29 (q, CH_3CH)
29.28 (d, C-5)
51.88 (q, CH_3OCO)
70.67 (t, CH_2Ph)
72.54 (d, C-3)
86.11 (d, C-4)
96.06 (t, OCH_2O)
127.40 (t, C-2')
127.59, 127.77, 128.43 (d, CH aromatics)

137.64 (s, CCH_2 aromatic)
139.55 (s, C-2)
167.19 (s, C-1)

Major isomer: *syn* **(139 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.95-1.01 (6 H, d, $[CH_3]_2CH$)
1.93 (1 H, m, H-5)
3.01 (1 H, broad s, O*H*)
3.58 (1 H, dd, *J* 5.5 and 3.6 Hz, H-4)
3.73 (3 H, s, CH_3OCO)
4.57 (1 H, m, H-3)
4.62 (2 H, s, CH_2Ph)
4.72 and 4.76 (2 H, AB system, *J* 7.2 Hz, OCH_2O)
5.95 (1 H, t, *J* 1.4 Hz, H_B)
6.32 (1 H, t, *J* 1.0 Hz, H_A)
7.29 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

17.79 (q, CH_3CH)
19.49 (q, CH_3CH)
30.42 (d, C-5)
51.79 (q, CH_3OCO)

70.28 (t, CH_2Ph)
70.87 (d, C-3)
86.07 (d, C-4)
96.23 (t, OCH_2O)
126.38 (t, C-2')
127.67, 127.77, 128.43 (d, CH aromatics)
137.46 (s, CCH_2 aromatic)
141.46 (s, C-2)
166.47 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.121

m/z (EI):

217(M^+-91, 0.1), 174(1.2), 159(9.8), 115(63.5), 91(100), 89(4.4), 77(4.1), 65(12.8) and 43(2.4).

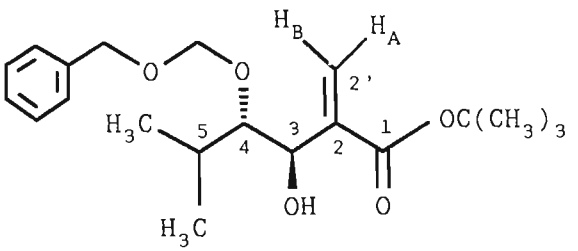
$C_{17}H_{24}O_5$ (308.38) Calculated: C 66.21 H 7.84
Found (mixture): C 66.18 H 8.18

tert-Butyl 4-[(benzyloxy)methoxy]-3-hydroxy-5-methyl-2-methylenehexanoate **(140)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(108)** (1.419 g, 6.38 mmol), *tert*-butyl acrylate **(86 C)** (3.271 g, 25.52 mmol) and DABCO **(56)** (0.716 g, 6.38 mmol), using hexane-ethyl acetate (93:7) as eluant, furnished the pure diastereomeric mixture (1.186 g, **53%**).

$C_{20}H_{30}O_5$ **MW** 350.46

Minor isomer: *anti* **(140 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

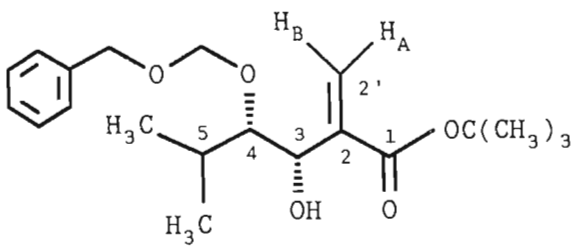
0.96-1.04 (6 H, d, $[CH_3]_2CH$)
1.49 (9 H, s, $[CH_3]_3C$)
1.93 (1 H, m, H-5)
3.65 (1 H, dd, *J* 6.0 and 4.2 Hz, H-4)
3.10 (1 H, broad s, O*H*)
4.48-4.60 (1 H, m, H-3)
4.61 (2 H, s, CH_2Ph)
4.71 and 4.78 (2 H, AB system, *J* 6.8 Hz, OCH_2O)
5.86 (1 H, t, *J* 1.3 Hz, H_B)
6.22 (1 H, dd, *J* 1.7 and 0.5 Hz)
7.34 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.03 (q, CH_3CH)
20.40 (q, CH_3CH)
28.01 (q, $[CH_3]_3C$)
29.11 (d, C-5)
70.08 (t, CH_2Ph)
72.57 (d, C-3)
81.40 (s, $OC[CH_3]_3$)
85.61 (d, C-4)
95.87 (t, OCH_2O)
126.26 (t, C-2')

127.69, 127.79, 128.41 (d, CH aromatics)
137.53 (s, CCH_2 aromatic)
140.99 (s, C-2)
165.31 (s, C-1)

Major isomer: *syn* **(140 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.96-1.04 (6 H, d, $[CH_3]_2CH$)
1.49 (9 H, s, $[CH_3]_3C$)
1.93 (1 H, m, H-5)
3.10 (1 H, broad s, O*H*)
3.55 (1 H, dd, *J* 5.5 and 3.7 Hz, H-4)
4.48-4.60 (1 H, m, H-3)
4.62 (2 H, s, CH_2Ph)
4.74 (2 H, s, OCH_2O)
5.85 (1 H, t, *J* 1.5 Hz, H_B)
6.24 (1 H, dd, *J* 1.5 and 0.9 Hz, H_A)
7.34 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.89 (q, CH_3CH)
19.66 (q, CH_3CH)
28.07 (q, $[CH_3]_3C$)

30.33 (d, C-5)
70.22 (t, CH_2Ph)
70.82 (d, C-3)
81.18 (s,$OC[CH_3]_3$)
86.22 (d, C-4)
96.35 (t, OCH_2O)
125.40 (t, C-2')
127.72, 127.79, 128.41 (d, CH aromatics)
137.53 (s, CCH_2 aromatic)
142.99 (s, C-2)
165.31 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.105

m/z (EI):

277(M^+-73, 0.5), 223(5.8), 222(5.3), 163(5.8), 101(25.8), 91(100), 77(3.5), 65(4.3), 73(1.2) and 43(1.1).

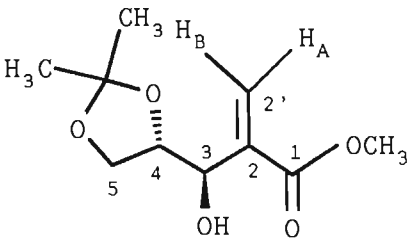
$C_{20}H_{30}O_{58}$ (350.46) Calculated: C 68.54 H 8.63
Found (mixture): C 68.27 H 8.52

(3S, 4R) and (3R, 4R)-Methyl 3-hydroxy-4,5-(isopropylidene-dioxy)-2-methylenepentanoate **(141)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(20)** (1.13 g, 8.68 mmol), methyl acrylate (0.86 ml, 9.55 mmol) and DABCO **(56)** (0.089 g, 0.87 mmol), using hexane-ethyl acetate (70:30) as eluant, afforded the major (*anti*) diastereomer and the pure diastereomeric mixture (1.164 g, **62%**).

$C_{10}H_{16}O_5$ **MW** 216.24

Major isomer: *anti* **(141 A)**



$[\alpha]_D^{29.5}$: -6.47° (*c* 0.77, $CHCl_3$)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

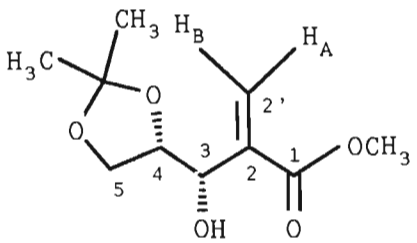
1.35 (3 H, s, CH_3C)
1.44 (3 H, s, CH_3C)
3.12 (1 H, d, *J* 4.9 Hz, O*H*)
3.79 (3 H, s, CH_3O)
3.93 (2 H, d, *J* 6.3 Hz, H-5)
4.35 (1 H, m, H-4)
4.55 (1 H, m, H-3)
6.01 (1 H, t, *J* 1.3 Hz, H_B)
6.37 (1 H, t, *J* 1.0 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.11 (q, CH_3C)
26.11 (q, CH_3C)
52.19 (q, CH_3O)
65.27 (t, C-5)
71.18 (d, C-3)
76.84 (d, C-4)
110.05 (s, O*C*[CH_3]$_2$O)
127.97 (t, C-2')

138.53 (s, C-2)
167.07 (s, C-1)

Minor isomer: *syn* **(141 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.36 (3 H, s, CH_3C)
1.46 (3 H, s, CH_3C)
2.96 (1 H, d, *J* 6.9 Hz, O*H*)
3.79 (3 H, s, CH_3O)
3.89 (2 H, d, *J* 6.5 Hz, H-5)
4.01 (1 H, m, H-4)
4.50 (1 H, m, H-3)
5.99 (1 H, t, *J* 1.2 Hz, H_B)
6.39 (1 H, t, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.20 (q, CH_3C)
26.48 (q, CH_3C)
52.37 (q, CH_3O)
66.42 (t, C-5)
70.88 (d, C-3)
77.79 (d, C-4)
110.13 (s, $OC[CH_3]_2O$)

127.60 (t, C-2')
139.85 (s, C-2)
167.01 (s, C-1)

m/z (EI):

201(M^+-15, 11), 141(5), 127(7), 115(3), 101(100), 85(8), 83(15), 59(16) and 43(70).

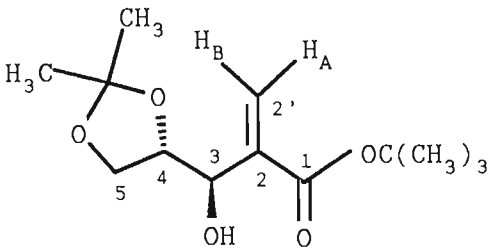
$C_{10}H_{16}O_5$ (216.24) Calculated: C 55.55 H 7.46
Found (mixture): C 55.54 H 7.59

tert-Butyl 3-hydroxy-4,5-(isopropylidenedioxy)-2-methylene-pentanoate **(66)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(20)** (1.41 g, 10.83 mmol), *tert*-butyl acrylate **(86 C)** (1.527 g, 11.91 mmol) and DABCO **(56)** (0.121 g, 1.08 mmol), using hexane-ethyl acetate (75:25) as eluant, furnished the pure major (*anti*) diastereomer, the pure diastereomeric mixture and the minor (*syn*) diastereomer (1.707 g, **61%**).

$C_{13}H_{22}O_5$ **MW** 258.32

Major isomer: *anti* **(66 A)**



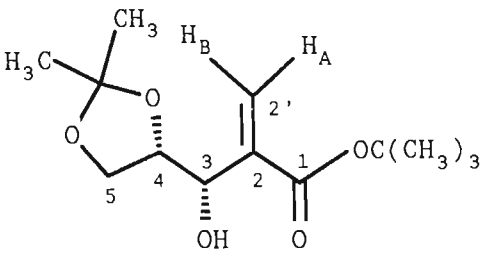
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.36 (3 H, s, CH_3C)1
1.44 (3 H, s, CH_3C)
1.51 (9 H, s, $[CH_3]_3CO$)
3.16 (1 H, d, *J* 5.2 Hz, O*H*)
3.92 and 3.96 (2 H, dd, *J* 6.3 and 0.7 Hz, H-5)
4.34 (1 H, dt, *J* 6.3 and 0.6 Hz, H-4)
4.48 (1 H, m, H-3)
5.89 (1 H, t, *J* 1.4 Hz, H_B)
6.26 (1 H, dd, *J* 1.4 and 0.8 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.23 (q, CH_3C)
26.68 (q, CH_3C)
28.16 (q, $OC[CH_3]_3$)
65.50 (t, C-5)
71.55 (d, C-3)
76.93 (d, C-4)
81.97 (s, $OC[CH_3]_3$)
110.00 (s, $OC[CH_3]_2O$)
126.92 (t, C-2')
139.89 (s, C-2)
165.97 (s, C-1)

Minor isomer: *syn* **(66 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.38 (3 H, s, CH_3C)
1.47 (3 H, s, CH_3C)
1.51 (9 H, s, $[CH_3]_3C$)
2.87 (1 H, d, *J* 8.3 Hz, O*H*)
3.86 and 4.02 (2 H, ABX system, J_{AB} 8.4; J_{AX} 6.5 Hz and J_{BX} 6.8 Hz, H-5)
4.27 (1 H, dt, *J* 6.6 and 4.7 Hz, H-4)
4.43 (1 H, m, H-3)
5.88 (1 H, t, *J* 1.1Hz, H_B)
6.28 (1 H, dd, *J* 1.3 and 0.5 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.37 (q, CH_3C)
26.54 (q, CH_3C)
28.14 (q, $[CH_3]_3C$)
66.40 (t, C-5)
71.10 (d, C-3)
78.32 (d, C-4)
81.77 (s, $OC[CH_3]_3$)
110.08 (s, $OC[CH_3]_2O$)
126.47 (t, C-2')
141.36 (s, C-2)
165.87 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.077

m/z (EI):

243(M^+-15, 0.5), 185(3.8), 142(0.3), 127(7.6), 101(100), 85(2.0), 73(9.8), 57(18.6) and 43(25.6).

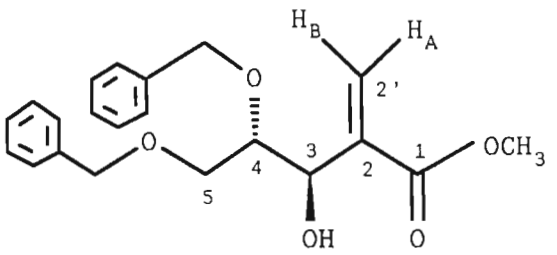
$C_{13}H_{22}O_5$ (258.32) Calculated: C 60.45 H 8.58
Found (mixture): C 60.74 H 8.78

Methyl 4,5-dibenzyloxy-3-hydroxy-2-methylenepentanoate **(127)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(115)** (0.410 g, 1.52 mmol), methyl acrylate (0.55 ml, 6.08 mmol) and DABCO **(56)** (0.171 g, 1.52 mmol), using hexane-ethyl acetate (93:7) as eluant, furnished the pure diastereomeric mixture (0.184 g, **34%**).

$C_{21}H_{24}O_5$ **MW** 356.42

Major isomer: *anti* **(127 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

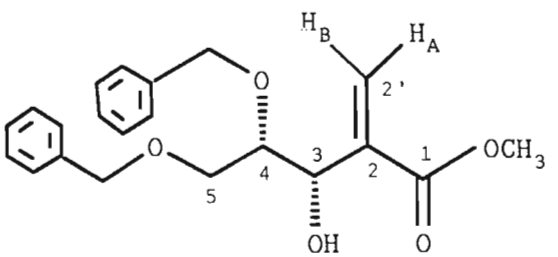
3.46 (1 H, d, *J* 5.9 Hz, O*H*)
3.66 (3 H, s, CH_3)
3.62-3.76 (2 H, m, H-5)
3.80-3.88 (1 H, m, H-4)
4.53 (2 H, s, PhCH_2OCH_2)
4.65 and 4.71 (2 H, AB system, J_{AB} 11.8 Hz, PhCH_2OCH)
4.76 (1 H, m, H-3)
5.95 (1 H, t, *J* 1.5 Hz, H_B)
6.31 (1 H, t, *J* 1.2 Hz, H_A)
7.30 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

51.91 (q, CH_3)
69.69 (t, C-5)
71.68 (d, C-3)
72.33 (t, PhCH_2OCH_2)
73.66 (t, PhCH_2OCH)
79.02 (d, C-4)
127.04 (t, C-2')
128.00, 128.05, 128.29, 128.43, 128.68 (d, *C*H aromatics)
138.26 (s, *C*CH_2 aromatic)
138.52 (s, *C*CH_2 aromatic)
139.56 (s, C-2)

167.11 (s, C-1)

Minor isomer: *syn* **(127 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.23 (1 H, d, *J* 7.0 Hz, O*H*)
3.66 (3 H, s, CH_3)
3.62-3.76 (2 H, m, H-5)
3.80-3.88 (1 H, m, H-4)
4.45 and 4.52 (2 H, AB system, J_{AB} 11.5 Hz, PhCH_2OCH_2)
4.64 (2 H, s, PhCH_2OCH)
4.76 (1 H, m, H-3)
5.97 (1 H, t, *J* 1.4 Hz, H_B)
6.33 (1 H, t, *J* 1.2 Hz, H_A)
7.30 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

51.92 (q, CH_3)
70.76 (t, C-5)
71.21 (d, C-3)
73.43 (t, PhCH_2OCH_2)
73.63 (t, PhCH_2OCH)
78.52 (d, C-4)
126.88 (t, C-2')

128.00, 128.05, 128.29, 128.43, 128.68 (d, *C*H aromatics)
138.26 (s, *C*CH_2 aromatic)
140.38 (s, *C*CH_2 aromatic)
140.38 (s, C-2)
167.07 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.139

m/z (EI):

107(M^+-249, 3), 91(100), 77(4) and 65(16).

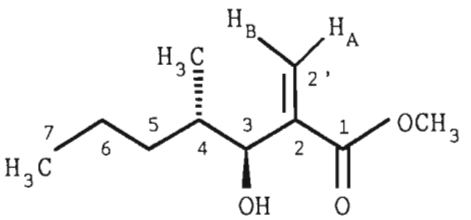
$C_{21}H_{24}O_5$ (356.42) Calculated: C 70.77 H 6.79
Found (mixture): C 70.77 H 6.83

Methyl 3-hydroxy-4-methyl-2-methyleneheptanoate **(142)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(122)** (5.00 g, 49.92 mmol), methyl acrylate (7.19 ml, 79.87 mmol) and DABCO **(56)** (0.560 g, 4.99 mmol)/(±)-3-quinuclidinol **(71)** (1.904 g, 14.97 mmol), using hexane-ethyl acetate (95:5) as eluant, to *1 g* of crude product, furnished the pure diastereomeric mixture (0.694 g, **29%**).

$C_{10}H_{18}O_3$ **MW** 186.25

Minor isomer: *anti* **(142 A)**



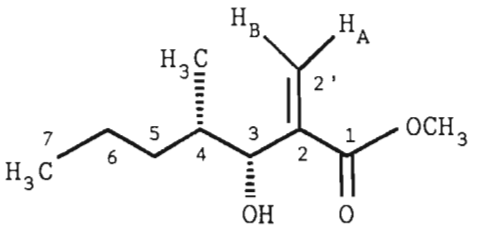
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.82-0.93 (6 H, m, C*H*$_3$CH and H-7)
1.03-1.65 (4 H, m, H-5 and H-6)
1.75 (1 H, m, H-4)
2.73 (1 H, broad s, O*H*)
3.78 (3 H, s, C*H*$_3$O)
4.13 (1 H, m, H-3)
5.76 (1 H, t, *J* 1.2 Hz, H_B)
6.26 (1 H, d, *J* 1.3 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

14.37 (q, C-7)
16.44 (q, *C*H$_3$CH)
20.16 (t, C-6)
33.81 (t, C-5)
37.47 (d, C-4)
51.83 (q, *C*H$_3$O)
76.46 (d, C-3)
126.29 (t, C-2')
141.25 (s, C-2)
167.25 (s, C-1)

Major isomer: *syn* **(142 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.82-0.93 (6 H, m, CH_3CH and H-7)
1.03-1.65 (4 H, m, H-5 and H-6)
1.75 (1 H, m, H-4)
2.49 (1 H, broad s, O*H*)
3.77 (3 H, s, CH_3O)
4.32 (1 H, m, H-3)
5.81 (1 H, t, *J* 1.3 Hz, H_B)
6.29 (1 H, dd, *J* 1.4 and 0.7 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

13.62 (q, C-7)
14.22 (q, CH_3CH)
20.22 (t, C-6)
36.05 (t, C-5)
36.66 (d, C-4)
51.83 (q, CH_3O)
75.01 (d, C-3)
125.68 (t, C-2')
141.73 (s, C-2)
167.06 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.016

m/z (EI):

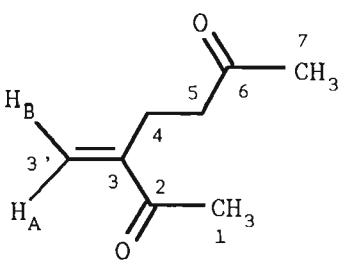
169(M^+-17, 0.1), 168(0.3), 155(1.0), 139(1.7), 115(100), 84(75.7), 71(6.9), 59(3.5), 56(17.0) and 43(12.5).

$C_{10}H_{18}O_3$ (186.25) Calculated: C 64.49 H 9.74
Found (mixture): C 64.71 H 9.93

5.2.8 THE DIMER OF MVK.

3-Methylene-heptan-2,6-dione **(143)**

Isolated as a by-product from those coupling reactions where methyl vinyl ketone was utilised. Purification was effected by flash chromatography, using hexane-ethyl acetate as eluant.



$C_8H_{12}O_2$ **MW** 140.18

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.14 (3 H, s, H-1/H-7)
2.34 (3 H, s, H-1/H-7)
2.56 (4 H, m, H-4 and H-5)

5.85 (1 H, m, H_B)
6.05 (1 H, m, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

25.21 (t, C-4)
25.86 (q, C-1/C-7)
29.85 (q, C-1/C-7)
42.38 (t, C-5)
126.31 (t, C-3')
147.62 (s, C-3)
199.47 (s, C-2/C-6)
207.84 (s, C-2/C-6)

m/z (EI):

140(M^+, 0.4), 125(43.6), 97(75.9), 69(3.3), 54(3.1) and 43(100).

$C_8H_{12}O_2$ (140.18) Calculated: C 68.55 H 8.63
Found: C 68.34 H 8.47

5.2.9 THE α-METHYLENE-γ-BUTYROLACTONES.

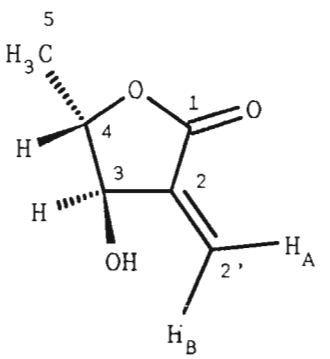
3-hydroxy-4-methyl-2-methylene-γ-butyrolactone **(65)**

Concentrated hydrochloric acid (1.63 ml, 14.29 mmol) was added to a solution of the diastereomeric mixture **(134)** (0.69 g, 2.46 mmol) in acetic acid-water (4:1 mixture, 14.60 ml:3.65 ml). The reaction mixture was stirred overnight at room temperature. Sodium acetate (3.52 g, 42.93 mmol) was added, the mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, using hexane-ethyl acetate (55:45) as

eluant. Further purification by flash chromatography, using hexane-ethyl acetate (85:15) as eluant, furnished the pure minor (*syn*) lactone **(65 B)** and the mixture of the two lactones **(65 A/B)** (0.09 g, 29%).

$C_6H_8O_3$ **MW** 128.13

anti lactone **(65 A)**



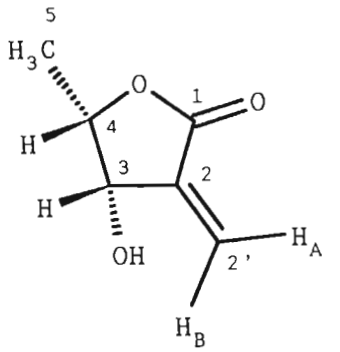
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.41 (3 H, d, *J* 6.5 Hz, CH_3)
3.16 (1 H, broad s, O*H*)
4.67 (1 H, dq, *J* 6.5 and 5.8 Hz, $CHCH_3$)
4.84 (1 H, m, C*H*OH)
6.01 (1 H, d, *J* 1.7 Hz, H_B)
6.40 (1 H, d, *J* 2.2 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

14.26 (q, CH_3)
69.49 (d, *C*HOH)
78.88 (d, $CHCH_3$)
126.58 (t, CH_2)
138.64 (s, CCH_2)
169.60 (s, *C*OO)

syn lactone **(65 B)**



$[\alpha]_D^{22}$: +4.26° (*c* 0.19, MeOH)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.44 (3 H, d, *J* 6.3 Hz, CH_3)
3.72 (1 H, broad s, O*H*)
4.42 (1 H, dq, *J* 6.4 and 4.4 Hz, $CHCH_3$)
4.46 (1 H, m, C*H*OH)
5.99 (1 H, d, *J* 2.0 Hz, H_B)
6.39 (1 H, d, *J* 2.2 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

19.04 (q, CH_3)
74.16 (d, CHOH)
82.12 (d, $CHCH_3$)
126.17 (t, CH_2)
138.75 (s, CCH_2)
169.34 (s, COO)

m/z (EI):

128(M^+, 0.2), 113(0.4), 84(100), 55(24.6), 43(6.7), 29(6.2), 28(3.1) and 26(2.9).

$C_6H_8O_3$ (128.13) Calculated: C 56.25 H 6.29
Found: No satisfactory analysis.

5.2.10 THE *N*-PROTECTED α-AMINO ALDEHYDES.

5.2.10.1 THE *N,N*-DIBENZYLAMINO ALDEHYDES.

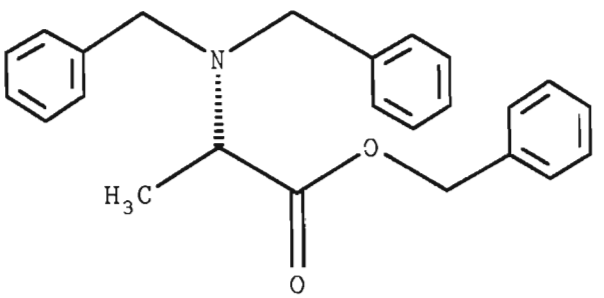
GENERAL PROCEDURE 6:

N-Alkylation and esterification of the amino acids.

The amino acid (1 equivalent) was added to a solution of potassium carbonate (2 equivalents) and sodium hydroxide (2 equivalents) in water (190 ml/225 mmol NaOH). The solution was heated to reflux temperature and benzyl bromide (3.02 equivalents) was added dropwise. Reflux was continued for a further 30 min. The reaction mixture was cooled and extracted with diethyl ether. The ethereal layer was washed with brine, dried and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography.

(S)-Benzyl 2-(N,N-dibenzylamino)propanoate **(182)**

Application of **GENERAL PROCEDURE 6** to (L)-alanine **(173a)** (10.00 g, 112.25 mmol), using hexane-ethyl acetate (95:5) as eluant, afforded the title compound (27.58 g, **68%**).



$C_{24}H_{25}NO_2$ **MW** 359.47

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.32 (3 H, d, *J* 7.1 Hz, CH_3)
3.55 (1 H, q, *J* 7.1 Hz, $CHCH_3$)
3.62 and 3.81 (4 H, AB system, J_{AB} 14.0 Hz, 2 × NCH_2)
5.10 and 5.20 (2 H, AB system, J_{AB} 12.3 Hz, OCH_2)
7.26 (15 H, m, 2 × $NCH_2C_6H_5$ and $OCH_2C_6H_5$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

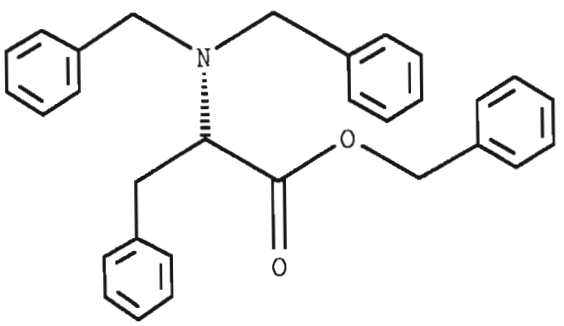
14.88 (q, CH_3)
54.49 (t, NCH_2)
56.26 (d, $CHCH_3$)
66.09 (t, OCH_20
127.24, 128.54, 128.61, 128.86, 128.94 (d, CH aromatics)
140.14 (s, CCH_2 aromatic)
173.87 (s, COO)

m/z (EI):

359(M^+, 0.3), 282(0.1), 268(0.4), 224(92.0), 105(2.0), 91(100), 77(1.7) and 65(7.9).

(S)-Benzyl 2-(N,N-Dibenzylamino)-3-phenylpropanoate **(183)**

Application of **GENERAL PROCEDURE** 6 to (L)-phenylalanine **(181)** 7.56 g, 45.77 mmol), using hexane-ethyl acetate (95:5) as eluant, afforded the title compound (14.87 g, **78%**).



$C_{30}H_{29}NO_2$ **MW** 435.57

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.99 and 3.14 (2 H, ABX system, J_{AB} 14.0 Hz; J_{AX} 7.3 Hz; J_{BX} 8.2 Hz, $PhCH_2CH$)
3.53 and 3.92 (4 H, AB system, J_{AB} 14.0 Hz, 2 × NCH_2)
3.72 (1 H, t, *J* 7.8 Hz, *CH*N)
5.11 and 5.23 (2 H, AB system, J_{AB} 12.3 Hz, OCH_2)
7.19 (20 H, m, 2 × $NCH_2C_6H_5$, $C_5H_6CH_2$ and $OCH_2C_6H_5$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

35.74 (t, CH_2CH)
54.51 (t, NCH_2)
62.51 (d, $CHCH_2$)
66.23 (t, OCH_2)
126.61, 127.25, 128.49, 128.64 (d, *C*H aromatics)
128.80, 128.91, 129.03, 129.80 (d, *C*H aromatics)
136.33, 138.42, 139.59 (s, *C*CH_2 aromatics)

172.62 (s, COO)

m/z (EI):

344(M^+-91, 20), 300(15), 208(1), 132(1), 105(1), 91(100), 77(2) and 65(9).

GENERAL PROCEDURE 7:

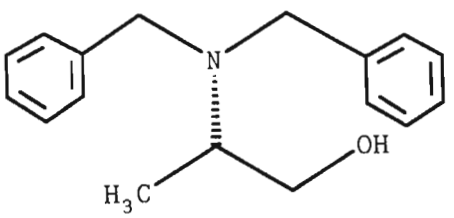
Reduction of the amino esters with lithium aluminium hydride.

A solution of the ester (1 equivalent) in diethyl ether (75 ml/39 mmol) was added dropwise to a suspension of lithium aluminium hydride (1.19 equivalents) in diethyl ether (50 ml/47 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h. The mixture was treated sequentially with water (1.77 ml/47 mmol $LiAlH_4$), 15% sodium hydroxide (1.77 ml) and water (1.77 ml). The aluminium salts were filtered off and thoroughly washed with diethyl ether. The salts were dissolved in dilute (2 N) sulfuric acid and the mixture was extracted with diethyl ether. The combined ethereal layers were washed with brine, dried and concentrated under reduced pressure to afford the crude product, which also contained some benzyl alcohol. Distillation *in vacuo* removed most of the benzyl alcohol. The residue was purified by flash chromatography.

(S)-2-(N,N-Dibenzylamino)propanol **(184)**

Application of **GENERAL PROCEDURE 7** to the ester **(182)** (14.0 g, 38.95 mmol), using hexane-ethyl acetate (95:5) as eluant,

afforded the title compound (7.17 g, **72%**).



$C_{17}H_{21}NO$ **MW** 255.36

m.p.: 40-42°C (Lit.,[174] 39°C).

$[\alpha]_D^{30.4}$: +78.8° (*c* 0.53, CH_2Cl_2) [Lit.,[174] $[\alpha]_D^{20}$ +80.6° (*c* 1.85, CH_2Cl_2)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.96 (3 H, d, *J* 6.7 Hz, CH_3)
2.97 (2 H, m, $CHCH_3$ and CH_2OH)
3.33 and 3.80 (2 H, m, CH_2O)
7.26 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

8.64 (q, CH_3)
52.85 (t, NCH_2)
54.09 (d, $CHCH_3$)
62.65 (t, CH_2O)
127.15, 128.43, 128.92 (d, CH aromatics)
139.23 (s, CCH_2 arcmatic)

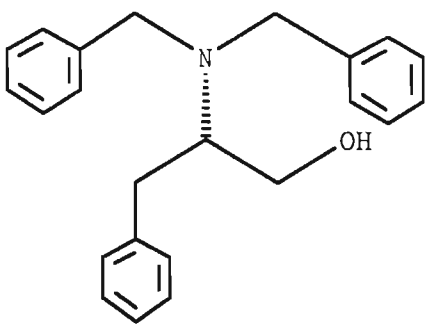
m/z (EI):

255(M^+, 0.1), 224(46.0), 91(100), 77(2.0), 65(12.3) and

31(0.9).

(S)-2-(N,N-Dibenzylamino)-3-phenylpropanol **(185)**

Application of **GENERAL PROCEDURE 7** to the ester **(183)** (14.70 g, 33.75 mmol), hexane-ethyl acetate (95:5) as eluant, afforded the title compound (9.75 g, **87%**).



$C_{23}H_{25}NO$ **MW** 331.46

m.p.: 65-68°C (Lit.,[174] 68°).

$[\alpha]_D^{24.1}$: +31.56° (*c* 0.77, CH_2Cl_2) [Lit.,[174] $[\alpha]_D^{20}$ +35.6° (*c* 1.91, CH_2Cl_2)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.42 (1 H, m, C_6H_5CH)
2.85 (1 H, broad s, OH)
3.09 (2 H, m, C_6H_5CH and NCH)
3.32 (1 H, m, CHOH)
3.50 (1 H, m, CHOH)
3.47 and 3.91 (4 H, AB system, J_{AB} 13.3 Hz, NCH_2)
7.21 (15 H, m, 2 × $NCH_2C_6H_5$ and $C_6H_5CH_2$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

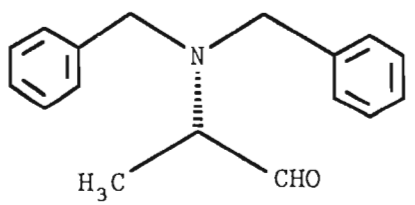
31.70 (t, $C_6H_5CH_2$)
53.20 (t, NCH_2)
60.32 (d, $CHCH_2$)
126.21, 127.28, 128.51, 128.98 (d, CH aromatics)
139.03, 139.12 (s, CCH_2)

m/z (EI):

331(M^+, 0.03), 300(11.62), 240(42.22), 118(1.69), 91(100), 77(3.07), 65(15.10) and 31(0.32).

(S)-2-(N,N-Dibenzylamino)propanal **(186)**

Application of **GENERAL PROCEDURE 3** to the alcohol **(184)** (7.68 g, 30.08 mmol) afforded the crude aldehyde (5.65 g, **74%**) which was used without further purification.



$C_{17}H_{19}NO$ **MW** 253.35

$[\alpha]_D^{21.8}$: -34.1° (*c* 1.00, CH_2Cl_2).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.15 (3 H, d, *J* 6.8 Hz, CH_3)
3.30 (1 H, q, *J* 6.8 Hz, $CHCH_3$)

3.53 and 3.71 (4 H, AB system, J_{AB} 13.6 Hz, 2 × NCH_2)
7.29 (10 H, m, 2 × C_6H_5)
9.71 (1 H, s, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

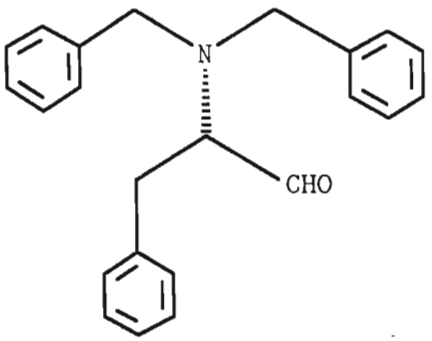
6.74 (q, $CHCH_3$)
55.04 (t, NCH_2)
62.99 (d, $CHCH_3$)
127.66, 128.75, 129.11 (d, CH aromatics)
139.38 (s, CCH_2 aromatic)
204.88 (d, CHCHO)

m/z (EI):

253(M^+, 0.1), 252(0.3), 224(65.1), 105(5.4), 91(100), 77(5.2), 65(36.7), 29(3.2) and 28(1.0).

(S)-2-(N,N-Dibenzylamino)-3-phenylpropanal **(187)**

Application of **GENERAL PROCEDURE 3** to the alcohol **(185)** (9.22 g, 27.82 mmol), using hexane-ethyl acetate (95:5) as eluant, afforded the title compound (7.944 g, **87%**).



$C_{23}H_{23}NO$ **MW** 329.45

$[\alpha]_D^{29.8}$: -73.55° (*c* 0.43, CH_2Cl_2) [Lit.,[174] $[\alpha]_D^{20}$ -89.9° (*c* 1.88, CH_2Cl_2)].

^{1}H n.m.r. (200 MHz: $CDCl_3$) δ/ppm:

2.93 and 3.14 (2 H, ABX system, J_{AB} 13.9 Hz; J_{AX} 7.2 Hz; J_{BX} 6.2 Hz, $C_6H_5CH_2$)
3.55 (1 H, t, *J* 7.2 Hz, $NCHCH_2$)
3.66 and 3.82 (4 H, AB system, J_{AB} 13.7 Hz, 2 × NCH_2)
7.23 (15 H, m, 2 × $NCH_2C_6H_5$ and $C_6H_5CH_2$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

30.10 (t, CH_2CH)
54.94 (t, NCH_2)
68.66 (d, $CHCH_2$)
126.58, 127.70, 128.77, 129.13, 129.81 (d, *C*H aromatics).
139.26, 139.52 (s, CCH_2 aromatics)
202.80 (d, CHCHO)

5.2.10.2. *N*-^{t}BOC-ALANINAL.

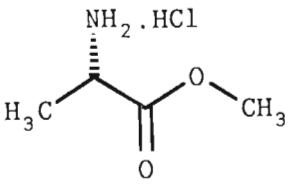
GENERAL PROCEDURE 8:

Reduction of the amino esters with diisobutylaluminium hydride.

A solution of the amino ester (1 equivalent) in dichloromethane-pentane (1:2.95 v/v) (95 ml $CHCl_2$/27 mmol ester) was cooled to -78°C. A 1.0 M solution of diisobutylaluminium hydride in hexane (2.10 equivalents) was added dropwise. The reaction was quenched with methanol after 10 min. The mixture was poured into a saturated solution of sodium potassium tartrate. Stirring was continued for another 30 min., followed by extraction with ethyl acetate. The organic phase was dried and concentrated under reduced pressure to afford the crude aldehyde.

(S)-Methyl 2-aminopropanoate-hydrochloride **(194a)**

Trimethylsilylchloride (34.61 ml, 272.70 mmol) was added to a suspension of (L)-alanine **(173a)** (15.98 g, 179.37 mmol) in methanol (150 ml). The solution was stirred for 10 h. The solvent was removed under reduced pressure and the precipitate was thoroughly washed with diethyl ether to afford the hydrochloride (22.77 g, **91%**).



$C_4ClH_{10}NO_2$ **MW** 139.58

m.p.: 102°C (Lit.,[210] 108°C).

^{1}H n.m.r. (200 MHz; D_2O/*not referenced*) δ/ppm:

1.47 (3 H, d, *J* 7.3 Hz, CH_3CH)
3.76 (3 H, s, OCH_3)
4.13 (1 H, q, *J* 7.3 Hz, *CH*)

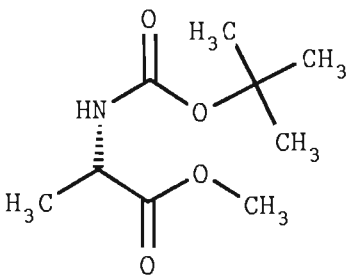
^{13}C n.m.r. (50 MHz; D_2O/*not referenced*) δ/ppm:

17.65 (q, CH_3CH)
51.44 (q, OCH_3)
56.24 (d, *C*H)
174.29 (s, *C*OO)

(S)-Methyl 2-{[(tert-butyloxy)carbonyl]amino}propanoate
(195a)

The amine hydrochloride **(194a)** (22.77 g, 163.23 mmol) and triethylamine (45.50 ml, 326.46 mmol) were added to dimethoxyethane (330 ml). Di-*tert*-butyl dicarbonate (38.80 g, 177.78 mmol) was added after 20 min. The mixture was stirred at room temperature for a further 25 min. The solution was poured into cold ethyl acetate and the pH was adjusted with dilute potassium hydrogen sulfate, (about 1.0

M), to between 2 and 3. The organic phase was separated, washed with water, dried and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, using hexane-ethyl acetate (96:4) as eluant, to afford the title compound (14.82 g, **45%**).



$C_9H_{17}NO_4$ **MW** 203.24

m.p.: 32-34°C (Lit.,[211] 33-34°C)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.39 (3 H, d, *J* 7.1 Hz, CH_3CH)
1.45 (9 H, s, $OC[CH_3]_3$)
3.75 (3 H, s, OCH_3)
4.32 (1 H, m, $CHCH_3$)
5.13 (1 H, m, NH)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

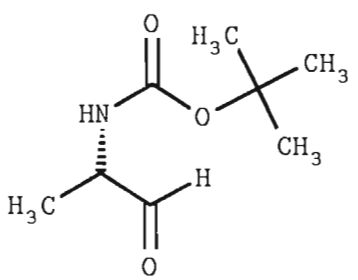
18.67 (q, CH_3CH)
28.40 (q, $OC[CH_3]_3$)
49.31 (d, $CHCH_3$)
52.48 (q, OCH_3)
80.07 (s, $OC[CH_3]_3$)
155.59 (s, NCO)
174.40 (s, $COOCH_3$)

m/z (EI):

203(M^+, 0.3), 188(0.13), 144(49.1), 116(5.7), 59(48.0), 57(100) and 44(33.6).

(S)-2-{[(tert-Butyloxy)carbonyl]amino}propanal **(179a)**

Application of **GENERAL PROCEDURE 8** to the ester **(195a)** (5.575 g, 27.43 mmol) afforded the crude product (4.835 g), which was used without further purification. A crude sample (0.300 g) was purified by flash chromatography, using hexane-ethyl acetate (95:5) as eluant, for analytical purposes. This afforded the title compound (0.160 g, **53%**).



$C_8H_{15}NO_3$ **MW** 173.21

m.p.: 84-88°C (Lit.,[165] 88-89°C).

[α]$_D^{rt}$: +34.7° (*c* 0.47, CH_2CL_2) [Lit.,[165] [α]$_D^{20}$ +36.7° (*c* 1.0, CH_2Cl_2)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.34 (3 H, d, *J* 7.3 Hz, CH_3CH)
1.42 (9 H, s, $C[CH_3]_3$)

4.21 (1 H, m, C*H*CH_3)
5.31 (1 H, m, N*H*)
9.57 (1 H, s, CHC*H*O)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.74 (q, *C*HCH_3)
28.29 (q, OC[CH_3]$_3$)
55.50 (d, *C*HCH_3)
80.02 (s, *C*[CH_3]$_3$)
155.39 (s, N*C*OO)
200.06 (d, CH*C*HO)

m/z (EI):

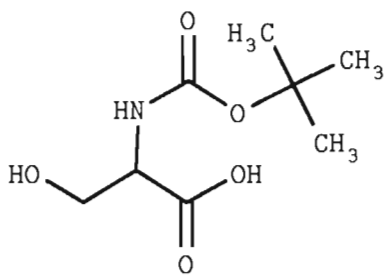
144(M^+-29, 17.8), 100(1.5), 89(7.2), 59(46.4) and 57(100).

5.2.10.3 THE DI-PROTECTED SERINAL.

(±)-2-(tert-Butyloxycarbonylamino)-3-hydroxypropanoic acid **(198)**

A solution of di-*tert*-butyl dicarbonate (12.86 g, 58.92 mmol) in dioxane (44 ml) was added to a stirred, ice-cold (~0-5°C) solution of (DL)-serine **(197)** (5.0 g, 47.58 mmol) in 1 N NaOH (98 ml). After 30 min. at this temperature, the stirred mixture was allowed to attain room temperature over 3.5 h. The mixture was concentrated to approximately half its volume by rotary evaporation at ~35°C, cooled in ice, then acidified to pH 2-3 by slow addition of cold 1 N potassium hydrogen sulfate (44 ml). The resulting mixture was extracted with ethyl acetate (3 × 160 ml). The organic

layer was dried and concentrated under reduced prssure to afford the crude product (8.00 g, **82%**) which was used without further purification.



$C_8H_{15}NO_5$ **MW** 205.21

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.47 (9 H, s, $C[CH_3]_3$)
3.95 (2 H, m, CH_2OH)
4.25 (1 H, m, CH)
5.98 (1 H, d, *J* 7.6 Hz, NH)
7.08 (2 H, broad s, OH and $COOH$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

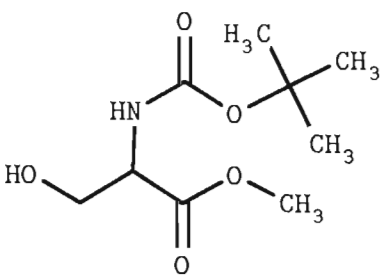
28.37 (q, $C[CH_3]_3$)
55.65 (d, NCH)
67.21 (t, CH_2OH)
80.79 (s, $C[CH_3]_3$)
156.75 (s, NCO)
174.44 (s, $COOH$)

m/z (EI):

190(M^+-15, 0.5), 175(0.8), 101(2.7), 73(0.8), 58(5.3) and 57(100).

(±)-Methyl 2 {[(tert-Butyloxy)carbonyl]amino}-3-hydroxy-propanoate **(199)**

The crude acid **(198)** (8.00 g, 38.99 mmol) was dissolved in diethyl ether (100 ml), cooled in an ice-bath and treated with 2 × 50 ml aliquots of cold 0.6 M ethereal diazomethane. After 30 min. at 0°C, the mixture was quenched with acetic acid. The resulting solution was washed with ~ 50% saturated $NaHCO_3$ solution (50 ml). The organic layer was washed with brine, dried and concentrated under reduced pressure to give the crude product (6.7 g, **82%**), which was used without further purification.



$C_9H_{17}NO_5$ **MW** 219.24

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.48 (9 H, s, $C[CH_3]_3$)
3.15 (1 H, broad s, O*H*)
3.78 (3 H, s, OCH_3)
3.92 (2 H, ABX system, J_{AB} 11.2 Hz, J_{AX} 3.6 Hz and J_{BX} 3.8 Hz, CH_2OH)
4.38 (1 H, t, *J* 3.7 Hz, C*H*)
5.65 (1 H, d, *J* 8.1 Hz, N*H*)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

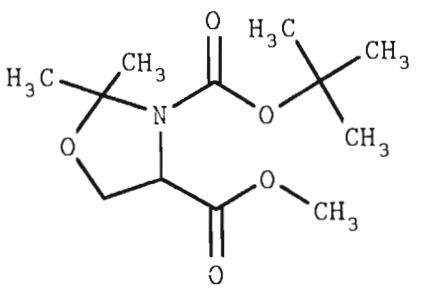
28.38 (q, $C[CH_3]_3$)
52.77 (q, OCH_3)
55.90 (d, CH)
63.44 (t, CH_2)
80.54 (s, $C[CH_3]_3$)
156.31 (s, NCOO)
172.05 (s, $COOCH_3$)

m/z (EI):

160(M^+-59, 23), 146(24), 118(12), 88(27), 73(2), 59(30) and 57(100).

(±)-(1,1-Dimethylethyl)-4-methyl-2,2-dimethyl-3,4-oxazolidinedicarboxylate **(200)**

A solution of the ester **(199)** (6.7 g, 30.59 mmol), 2,2-dimethoxypropane (8.0 ml, 65.06 mmol) and *p*-toluenesulfonic acid monohydrate (0.082 g, 0.43 mmol) in benzene (106 ml) was heated under reflux for 30 min.. The solvent was then removed by slow distillation until a volume of 90 ml had been collected. A further amount of 2,2-dimethoxypropane (2.0 ml, 16.27 mmol) and benzene (43 ml) was added and the procedure was repeated, collecting 34 ml of distillate. The cooled solution was diluted with diethyl ether (83 ml), washed with saturated $NaHCO_3$ (2 x 21 ml) and brine (17 ml). The organic layer was dried and concentrated under reduced pressure. The crude product was purified by flash chromatography, using hexane-ethyl acetate (75:25) as eluant. This yielded the title compound (6.33 g, **80%**). A sample was recrystallised for analytical purposes.



$C_{12}H_{21}NO_5$ **MW** 259.31

m.p.: 109-110°C (from hexane-CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) {values for corresponding *rotamer* in parenthesis} δ/ppm:

1.42 {1.50} (9 H, s, $C[CH_3]_3$)
1.54 (3 H, s, CH_3CN)
1.68 (3 H, s, CH_3CN)
3.76 (3 H, s, OCH_3)
4.11 (2 H, m, CH_2/CH)
4.38 (1 H, m, CH_2/CH)

^{13}C n.m.r. (50 MHz; $CDCl_3$) {values for corresponding *rotamer* in parenthesis} δ/ppm:

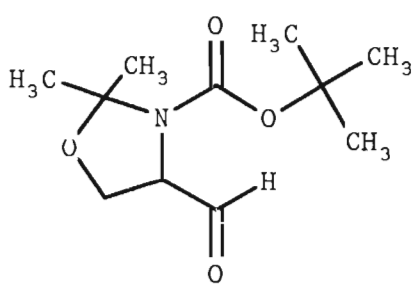
24.38 {25.16} (q, CH_3CN)
24.96 {26.03} (q, CH_3CN)
28.28 {28.35} (q, $C[CH_3]_3$)
52.31 {52.42} (q, OCH_3)
59.26 {59.20} (d, CH)
66.26 {66.01} (t, CH_2)
80.32 {80.90} (s, $C[CH_3]_3$)
95.04 {94.41} (s, $C[CH_3]_2$)
155.20 (s, NCOO)
171.71 (s, $COOCH_3$)

m/z (EI):

244(M^+-15, 7), 200(2), 158(1), 144(100), 100(4), 59(0.2) and 57(2).

(±)-1,1-Dimethylethyl-4-formyl-2,2-dimethyl-3-oxazolidine-carboxylate **(175)**

A 1.0 M solution of DIBAL-H in hexane (18.18 ml, 18.18 mmol) was added to a solution of the oxazolidine ester **(200)** (2.78 g, 10.73 mmol) in hexane (20 ml) at -78°C. The reaction mixture was stirred for an additional 2 h at this temperature, then quenched by slow addition of cold (-78°C) methanol (4.2 ml), while maintaining the internal temperature below -65°C. The resulting white emulsion was slowly poured into ice-cold 1 N HCl (69 ml) and the mixture was stirred for 15 min. The aqueous layer was extracted with ethyl acetate (3 x 69 ml). The combined organic layer was washed with brine, dried and concentrated under reduced pressure. Purification of the crude product by flash chromatography, using hexane-ethyl acetate (80:20) as eluant, furnished the title compound (0.77 g, **31%**).



$C_{11}H_{19}NO_4$ **MW** 229.28

^{1}H n.m.r. (200 MHz; $CDCl_3$) {values for corresponding *rotamer* in parenthesis} δ/ppm:

1.44 {1.52} (9 H, s, $C[CH_3]_3$)
1.51 {1.61} (3 H, s, CH_3CN)
1.56 {1.66} (3 H, s, CH_3CN)
4.10 {4.08} (2 H, d, *J* 2.8 Hz {*J* 2.3 Hz}, CH_2)
4.22 {4.35} (1 H, m, $CHCH_2$)
9.56 {9.62} (1 H, d, *J* 2.4 Hz {*J* 1.5 Hz}, CHCHO)

^{13}C n.m.r. (50 MHz: $CDCl_3$) {values for corresponding *rotamer* in parenthesis} δ/ppm:

23.79 {24.67} (q, CH_3CN)
25.79 {26.69} (q, CH_3CN)
28.27 {27.21} (q, $C[CH_3]_3$)
63.93 {63.47} (t, CH_2)
64.70 (d, CHN)
81.08 {81.37} (s, $C[CH_3]_3$)
95.08 {94.35} (s, $C[CH_3]_2$)
129.61 {127.80} (s, NCOO)
199.49 (d, CHCHO)

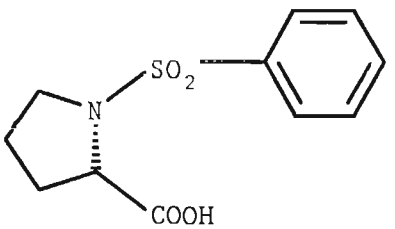
m/z (EI):

200(M^+-29, 4), 156(4), 101(2), 100(29), 98(3), 57(100), 56(5) and 55(2).

5.2.10.4 *N*-BENZENESULFONYL PROLINAL.

(S)-(N-Benzenesulfonyl)proline **(202)**

A solution of (L)-proline **(201)** (10.62 g, 92.24 mmol) in 1 N NaOH (190 ml) was treated with benzenesulfonyl chloride (12.10 ml, 94.84 mmol) and stirred for 40 h. The mixture was then acidified with 1 N HCl. The aqueous layer was extracted several times with diethyl ether. The combined ether layer was dried and concentrated under reduced pressure. The resulting crude product was purified by recrystallisation to yield the protected acid (15.23 g, **65%**) as a white solid.



$C_{11}H_{13}NO_4S$ **MW** 255.29

m.p.: 87-88°C (from hexane-CH_2Cl_2) (Lit.,[212] 84-86°C).

$[\alpha]_D^{21.0}$: -100.72° (*c* 0.49, MeOH) [Lit.,[175] $[\alpha]_D^{23}$ -45.2° (*c* 1.6, MeOH)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.70-2.13 (4 H, m, CH_2CH_2)
3.23-3.59 (2 H, m, NCH_2)
4.32 (1 H, m, NC*H*)

7.31-7.93 (5 H, m, C_6H_5)
10.09 (1 H, broad s, COOH)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

24.69 (t, NCH_2CH_2)
30.91 (t, CH_2CH)
48.82 (t, NCH_2)
60.53 (d, NCH)
127.79, 129.62, 133.53 (d, CH aromatics)
137.81 (s, CSO_2 aromatic)
177.82 (s, COOH)

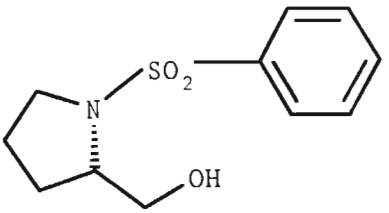
m/z (EI):

210(M^+-45, 100), 141(148), 77(67), 69(20), 65(3) and 45(2).

$C_{11}H_{13}NO_4S$ (255.29) Calculated: C 51.75 H 5.13 N 5.49
Found: C 51.71 H 5.44 N 5.40

(S)-(N-Benzenesulfonyl)prolinol **(203)**

The amino acid **(202)** (7.0 g, 27.42 mmol) was added to a suspension of lithium aluminium hydride (1.24 g, 32.74 mmol) in THF (20 ml). The mixture was stirred at room temperature for 2 h. Water (1.24 ml), 15% NaOH (1.24 ml) and water (3.72 ml) were successively added. The aluminium salts were filtered off and thoroughly washed with diethyl ether. The organic phase was dried and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography, using dichloromethane-methanol (99:1)as eluant. This afforded the title compound (4.27 g, **65%**).



$C_{11}H_{15}NO_3S$ **MW** 241.31

$[\alpha]_D^{21.4}$: -56.38° (*c* 0.49, CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.39-1.88 (4 H, m, CH_2CH_2)
3.07 (1 H, broad s, OH)
3.19-3.53 (2 H, m, NCH_2)
3.63 (1 H, m, NCH)
3.69 (2 H, d, *J* 4.1 Hz, CH_2OH)
7.51-7.89 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

24.18 (t, NCH_2CH_2)
28.73 (t, CH_2CH)
49.96 (t, NCH_2)
61.78 (d, NCH)
65.65 (t, CH_2OH)
127.53, 129.21, 132.98 (d, CH aromatics)
136.76 (s, CSO_2 aromatic)

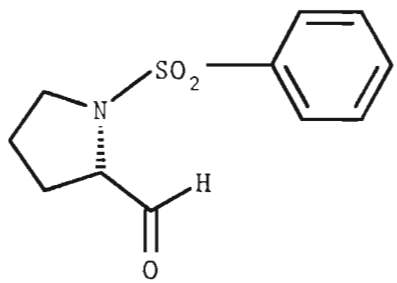
m/z (EI):

241(M^+, 0.14), 210(73.27), 141(44.11) and 77(100).

$C_{11}H_{15}NO_3S$ (241.31) Calculated: C 54.75 H 6.27 N 5.81
Found: C 54.43 H 6.18 N 5.65

(S)-(N-Benzenesulfonyl)prolinal **(204)**

Application of **GENERAL PROCEDURE 3** to the amino alcohol **(203)** (3.73 g, 15.46 mmol), (reaction time: *1.5 h*), using hexane-ethyl acetate (70:30) as eluant, afforded the title compound (2.02 g, **55%**).



$C_{11}H_{13}NO_3S$ **MW** 239.29

[α]$_D^{21.1}$: -164.86° (*c* 0.39, CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.59-2.15 (4 H, m, CH_2CH_2)
3.22 and 3.58 (2 H, m, NCH_2)
3.87 (1 H, m, NC*H*)
7.53-7.89 (5 H, m, C_6H_5)
9.68 (1 H, d, *J* 2.4 Hz, CHC*H*O)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

24.65 (t, NCH_2CH_2)
27.55 (t, CH_2CH)
49.19 (t, NCH_2)
66.55 (d, NCH)
127.58, 129.36, 133.32 (d, CH aromatics)
136.36 (s, CSO_2 aromatic)

199.94(d, CHCHO)

m/z (EI):

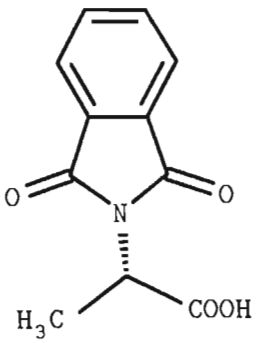
210(M^+-29, 79), 141(65), 97(3), 77(100), 69(4), 68(7), 55(1), 29(4) and 28(2).

$C_{11}H_3NO_3S$ (239.29) Calculated : C 55.21 H 5.48 N 5.86
Found: C 55.29 H 5.39 N 5.84

5.2.10.5. (*N*-PHTHALOYL)ALANINAL.

(S)-2-(N-Phthaloylamino)propanoic acid **(207)**

(L)-Alanine **(173a)** (10.0 g, 112.25 mmol) was added to a suspension of phthalic anhydride (16.67 g, 112.54 mmol) in toluene (35 ml). The mixture was refluxed overnight with azeotropic removal of water (Dean-Stark "trap"). After cooling, removal of the solvent afforded the crude acid (24.11 g, **98%**), which was used without further purification. An analytical sample was obtained by recrystallisation.



$C_{11}H_9NO_4$ **MW** 219.20

m.p.: 161-162°C (from hexane-methanol)

$[\alpha]_D^{20.2}$: -16.93° (*c* 0.44, absolute EtoH) [Lit.,[213] $[\alpha]_D^{20}$ -17.62° (*c* 3.355, absolute EtoH)].

^{1}H n.m.r. (200 MHz; CD_3COCD_3) δ/ppm:

1.69 (3 H, d, *J* 7.3 Hz, CH_3)
5.01 (1 H, q, *J* 7.4 Hz, $CHCH_3$)
7.83 (4 H, m, C_6H_4)
10.45 (1 H, broad s, COO*H*)

^{13}C n.m.r. (50 MHz; CD_3COCD_3) δ/ppm:

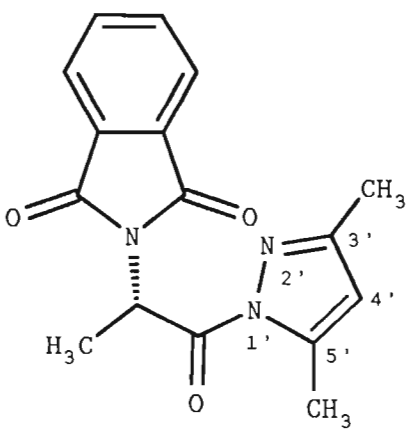
15.25 (q, CH_3)
47.82 (d, $CHCH_3$)
123.90 (d, *C*H aromatics)
129.60, 132.73 (s, *C*CO aromatics)
135.29 (d, *C*H aromatics)
167.93 (s, N*C*O)
171.23 (s, *C*OOH)

m/z (EI):

174(M^+-45, 100), 147(17), 104(12) and 76(11).

(S)-2-(N-Phthaloylamino)propanoic acid, 3,5-dimethylpyrazole **(208)**

A solution of the amino acid **(207)** (4.38 g, 20.00 mmol) and 3,5-dimethylpyrazole (2.31 g, 24.00 mmol) in chloroform (300 ml), was treated with a solution of dicyclohexylcarbodiimide (4.13 g, 20.00 mmol) in chloroform (100 ml) at -10°C over a period of 0.5 h, then stirred overnight at room temperature. The dicyclohexylurea was filtered off and the solvent ws removed under reduced pressure. The solid residue was taken up in ethyl acetate and sequentially washed with 1 N hydrochloric acid and water. The organic layer was dried and concentrated. The crude product was purified by recrystallisation.



$C_{16}H_{15}N_3O_3$ **MW** 297.32

m.p.: 120-121°C (from hexane-CH_2CL_2)

$[\alpha]_D^{25.0}$: -1.27° (*c* 0.47, CH_3COCH_3)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.89 (3 H, d, *J* 7.3 Hz, CH_3CH)
2.12 (3 H, s, C-5'Me)
2.53 (3 H, d, *J* 0.8 Hz, C-3'Me)
5.91 (1 H, q, *J* 7.3 Hz, $CHCH_3$)
5.92 (1 H, d, *J* 1.0 Hz, H-4')
7.70-7.88 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.74 (q, CH_3CH)
14.18 (q, C-5'CH_3)
15.65 (q, C-3'CH_3)
49.34 (d, CHN)
111.13 (d, C-4')
123.36, 134.02 (d, CH aromatics)
131.90 (s, NCOC aromatics)
144.56 (s, C-5')
152.66 (s, C-3')
167.74 (s, CONCH)
169.61 (s, COCH)

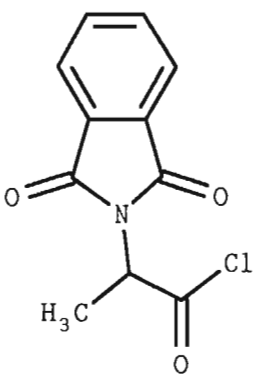
m/z (EI):

297(M^+, 2), 202(5), 174(100), 146(1), 132(20), 123(2), 122(3), 97(5), 95(7), 80(1), 76(19), 75(5), 74(2), 70(2), 65(3) and 42(2).

$C_{16}H_{15}N_3O_3$ (297.32) Calculated: C 64.64 H 5.09 N 14.13
Found: C 64.83 H 5.72 N 14.04

(±)-2-(N-Phthaloylamino)propanoyl chloride **(209)**

Thionyl chloride (8.72 ml, 119.53 mmol) was added to a mixture of the crude acid **(207)** (24.0 g, 109.49 mmol) in toluene (75 ml). The mixture was refluxed for 1 h., cooled and the solvent removed under reduced pressure. The residue was distilled *in vacuo* to afford the title compound (14.36 g, **55%**).



$C_{11}ClH_8NO_3$ **MW** 237.63

b.p.: 130-135°C/3.4 mm Hg.

m.p.: 61-63°C (Lit.,[214] 73°C).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.79 (3 H, d, *J* 7.2 Hz, CH_3)
5.18 (1 H, q, *J* 7.2 Hz, $CHCH_3$)
7.72-7.95 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.71 (q, CH_3)
56.20 (d, $CHCH_3$)
124.17 (d, CH aromatics)
131.82, 134.48 (s, CCO aromatics)

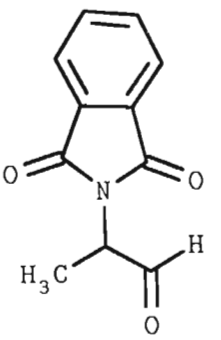
134.90 (d, CH aromatics)
166.97 (s, NCO)
172.31 (s, COCl)

m/z (EI):

174(M^+-64, 100), 130(33), 104(14), 77(10) and 76(21).

(±)-2-(N-Phthaloylamino)propanal **(188)**

A solution of the acid chloride **(209)** (14.26 g, 60.04 mmol) in anhydrous xylene (60 ml) was reduced in the presence of 5% $Pd/BaSO_4$ (2.28 g), at 110°C during 10 h, under hydrogen atmosphere (250 KPa/autoclave). The reaction mixture was cooled, the catalyst was filtered off and washed with diethyl ether. Removal of the solvent under reduced pressure afforded the crude aldehyde (14.42 g, **85%**), which was used without further purification. A homogenous sample was obtained by flash chromatography, using dichloromethane-methanol (90:10) as eluant.



$C_{11}H_9NO_3$ **MW** 203.20

m.p.: 109-112°C

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.62 (3 H, d, *J* 7.3 Hz, CH_3)
4.77 (1 H, q, *J* 7.3 Hz, $CHCH_3$)
7.76-7.92 (4 H, m, C_6H_4)
9.70 (1 H, s, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

12.94 (q, CH_3)
54.03 (d, $CHCH_3$)
123.64 (d, CH aromatics)
131.78 (s, CCO aromatics
134.40 (d, CH aromatics)
167.58 (s, CON)
196.93 (d, CHCHO)

m/z (EI):

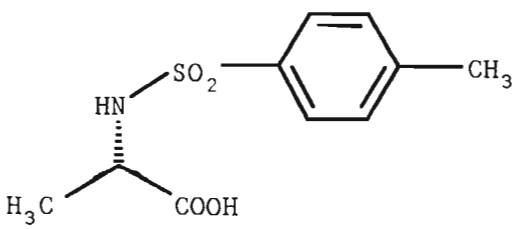
188(M^+-15, 0.1), 174(100), 146(4.2), 132(1.9), 130(24.0), 104(3.1), 102(2.4), 76(2.7), 75(0.7) and 50(0.4).

$C_{11}H_9NO_3$ (203.20) Calculated: C 65.02 H 4.46 N 6.90
Found: C 65.53 H 4.33 N 6.90

5.2.10.6 (*N*-TOSYL)ALANINAL.

(S)-2-(N-p-Toluenesulfonylamino)propanoic acid **(210)**

(L)-Alanine **(173a)** (7.0 g, 78.57 mmol) was added to a solution of sodium carbonate (24.98 g, 235.72 mmol) in water (157 ml). *p*-Toluenesulfonyl chloride (22.02 g, 115.50 mmol) was then added and the mixture was stirred overnight. It was then washed with diethyl ether. The aqueous phase was acidified with *conc*. HCl to pH 1-2, saturated with sodium chloride and extracted with dichloromethane. The organic layer was dried and removal of the solvent under reduced pressure afforded the crude product. Purification by recrystallisation gave the acid (10.47 g, **55%**) as a white solid.



$C_{10}H_{13}NO_4S$ **MW** 243.28

m.p.: 135-137°C (from hexane-CH_2Cl_2) (Lit.,[215] 133-134°C).

[α]$_D^{20.6}$: -14.22° (*c* 0.45, MeOH) [Lit.,[175] [α]$_D^{23}$ -15.68° (*c* 3.06, MeOH)].

^{1}H n.m.r. (200 MHz; CD_3COCD_3) δ/ppm:

1.34 (3 H, d, *J* 7.2 Hz, CH_3CH)
2.39 (3 H, s, $CH_3C_6H_4$)
3.98 (1 H, q, *J* 7.2 Hz, $CHCH_3$)
7.34 and 7.77 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; CD_3COCD_3) δ/ppm:

19.45 (q, CH_3CH)
21.42 (q, $CH_3C_6H_4$)
51.88 (d, $CHCH_3$)
127.91, 130.48 (d, *C*H aromatics)
139.10 (s, CCH_3 aromatic)
144.12 (s, SO_2C aromatic)
174.16 (s, *C*OOH)

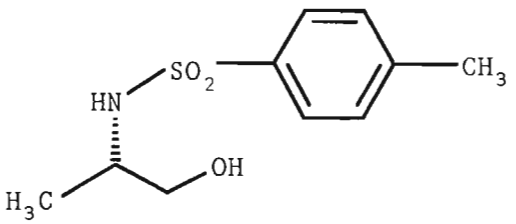
m/z (EI):

242(M^+-1, 2), 228(2), 213(19), 198(3), 155(4), 91(52), 73(100), 45(6) and 44(9).

(S)-2-(N-p-Toluenesulfonylamino)propanol **(211)**

The acid **(210)** (21.30 g, 87.65 mmol) was added to a suspension of lithium aluminium hydride (8.30 g, 218.69 mmol) in THF (115 ml). The mixture was refluxed overnight, cooled and water (8.3 ml) was added. 15% NaoH (8.3 ml) and water (24.9 ml) were successively added. The aluminium salts were filtered off and thoroughly washed with diethyl ether. The organic phase was dried and concentrated under reduced pressure. The crude product was purified by flash

chromatography using dichloromethane-methanol (99:1) as eluant. This yielded the alcohol (8.83 g, **44%**).



$C_{10}H_{15}NO_3S$ **MW** 229.30

m.p.: 60-63°C

$[\alpha]_D^{20.7}$: -4.38° (*c* 0.41, CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.99 (3 H, d, *J* 6.6 Hz, CH_3CH)
2.42 (3 H, s, $CH_3C_6H_4$)
3.03 (1 H, broad s, O*H*)
3.40 (2 H, m, CH_2OH)
3.54 (1 H, m, $CHCH_3$)
5.57 (1 H, d, *J* 7.1 Hz, N*H*)
7.30 and 7.79 (4 H, m, C_6H_4)

^{13}C n.m.r. ($CDCl_3$; 50 MHz) δ/ppm:

17.44 (q, CH_3CH)
21.52 (q, $CH_3C_6H_4$)
51.48 (d, $CHCH_3$)
66.14 (t, CH_2OH)
127.05, 129.74 (d, CH aromatics)
137.57 (s, CCH_3 aromatic)
143.46 (s, CSO_2 aromatic)

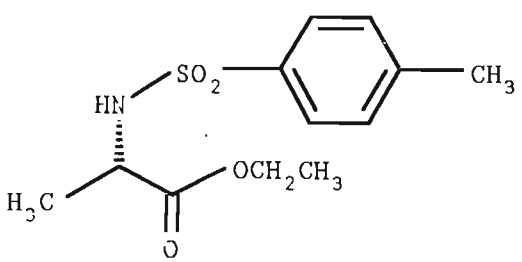
m/z (EI):

229(M^+, 0.4), 214(0.1), 198(63.3), 155(64.7), 91(100), 74(0.6), 44(1.5) and 31(1.8).

$C_{10}H_{15}NO_3S$ (229.30) Calculated: C 52.38 H 6.59 N 6.12
Found: C 52.65 H 6.59 N 6.22

(S)-Ethyl 2-(N-p-toluenesulfonylamino)propanoate **(215)**

A solution of the acid **(210)** 97.64 g, 31.44 mmol) in chloroform-ethanol (424:6 ml) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.917 g, 4.82 mmol) was refluxed overnight with removal of water (Dean-Stark "trap"). The cooled reaction mixture was concentrated under reduced pressure. The residue was taken up in chloroform, washed twice with 2 N Na_2CO_3, brine, dried and concentrated. Flash column chromatography, using hexane-ethyl acetate (85:15) as eluant, afforded the title compound (6.59 g, **77%**).



$C_{12}H_{17}NO_4S$ **MW** 271.33

m.p.: 66-67°C

$[\alpha]_D^{21.2}$: +10.23° (*c* 0.22, CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.13 (3 H, d, *J* 7.2 Hz, CH_3CH_2)
1.38 (3 H, d, *J* 7.2 Hz, CH_3CH)
2.42 (3 H, s, $CH_3C_6H_4$)
3.98 (2 H, q, *J* 7.1 Hz, OCH_2)
3.99 (1 H, q, *J* 7.1 Hz, $CHCH_3$)
5.36 (1 H, d, *J* 8.4 Hz, NH)
7.29 and 7.74 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.90 (q, CH_3CH_2)
19.89 (q, CH_3CH)
21.53 (q, $CH_3C_6H_4$)
51.52 (d, $CHCH_3$)
61.75 (t, OCH_2)
127.24, 129.65 (d, CH aromatics)
136.82 (s, CSO_2 aromatic)
143.63 (s, CCH_3 aromatic)
172.18 (s, COO)

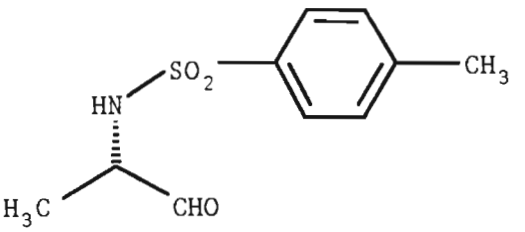
m/z (EI):

271(M^+, 1), 198(85), 155(81), 107(1), 91(100) and 44(1).

$C_{12}H_{17}NO_4S$ (271.33) Calculated: C 53.12 H 6.32 N 5.16
Found: C 53.04 H 6.50 N 4.92

(S)-2-(N-p-Toluenesulfonylamino)propanal **(212)**

Application of **GENERAL PROCEDURE 8** to the ester **(215)** (5.00 g, 18.45 mmol) afforded the crude aldehyde (4.12 g, **98%**) which was used without further purification.



$C_{10}H_{13}NO_3S$ **MW** 227.28

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.28 (3 H, d, *J* 7.4 Hz, CH_3CH)
2.42 (3 H, s, $CH_3C_6H_4$)
3.85 (1 H, m, $CHCH_3$)
5.78 (1 H, d, *J* 6.2 Hz, NH)
7.32 and 7.76 (4 H, m, C_6H_4)
9.45 (1 H, d, *J* 1.5 Hz, CHCHO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.85 (q, CH_3CH)
21.59 (q, $CH_3C_6H_4$)
57.47 (d, $CHCH_3$)
127.13, 129.90 (d, CH aromatics)
137.30 (s, CCH_3 aromatic)
143.58 (s, CSO_2 aromatic)
198.32 (d, CHCHO)

m/z (EI):

198(M^+-29, 68), 155(76), 107(1), 91(100) and 42(1).

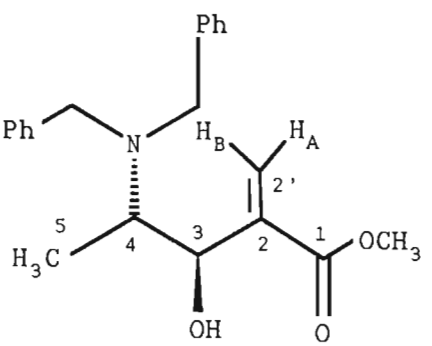
5.2.11. THE α-METHYLENE-β-HYDROXY-γ-AMINO ESTERS (AND BY-PRODUCTS).

Methyl 4 (N,N-dibenzylamino)-3-hydroxy-2-methylenepentanoate **(193)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(186)** (5.657 g, 22.33 mmol), methyl acrylate (8.04 ml, 89.32 mmol) and DABCO **(56)** (2.505 g, 22.33 mmol), using hexane ethyl acetate (93:7) as eluant, afforded the diastereomeric mixture (5.381 g, **71%**). The diastereomers were separated using hexane-ethyl acetate (96:4) as eluant.

$C_{12}H_{25}NO_3$ **MW** 339.44

Major isomer: *anti* **(193 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm;

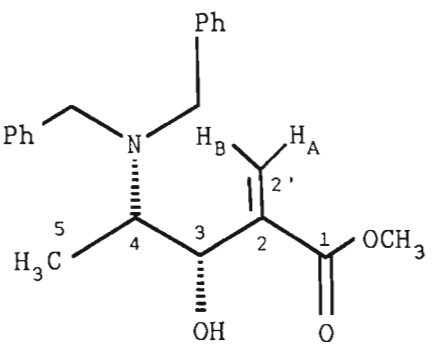
0.96 (3 H, d, *J* 6.8 Hz, H-5)
2.74 (1 H, dq, *J* 9.5 and 6.7 Hz, H-4)
3.33 and 3.89 (4 H, AB system, *J* 13.2 Hz, 2 × NCH_2)
3.65 (3 H, s, OCH_3)
4.46 (1 H, d, *J* 9.6 Hz, H-3)
5.73 (1 H, t, *J* 1.1 Hz, H_B)
6.24 (1 H, d, *J* 1.4 Hz, H_A)

7.28 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

8.12 (q, C-5)
51.73 (q, OCH_3)
53.26 (t, NCH_2)
59.86 (d, C-4)
69.76 (d, C-3)
127.36 (t, C-2')
127.29, 128.49, 129.10 (d, CH aromatics)
138.77 (s, CCH_2N aromatic)
141.36 (s, C-2)
166.97 (s, C-1)

Minor isomer: *syn* **(193 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.17 (3 H, d, *J* 6.7 Hz, H-5)
2.80 (1 H, broad s, O*H*)
3.03 (1 H, dq, *J* 7.8 and 6.7 Hz, H-4)
3.41 and 3.72 (4 H, AB system, J_{AB} 13.8 Hz, 2 × NCH_2)
3.56 (3 H, s, OCH_3)
4.37 (1 H, d, *J* 7.8 Hz, H-3)
5.72 (1 H, t, *J* 1.1 Hz, H_B)
6.25 (1 H, d, *J* 1.3 Hz, H_A)
7.26 (10 H. m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

8.84 (q, C-5)
51.82 (OCH_3)
54.15 (t, NCH_2)
56.63 (d, C-4)
75.37 (d, C-3)
127.14 (t, C-2')
127.20, 128.55, 129.16 (d, *C*H aromatics)
140.12 (s, CCH_2N aromatics)
141.46 (s, C-2)
167.41 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.136

m/z (EI):

308(M^+-31, 0.4), 224(45.4), 91(100), 77(1.0), 65(7.7) and 59(0.5).

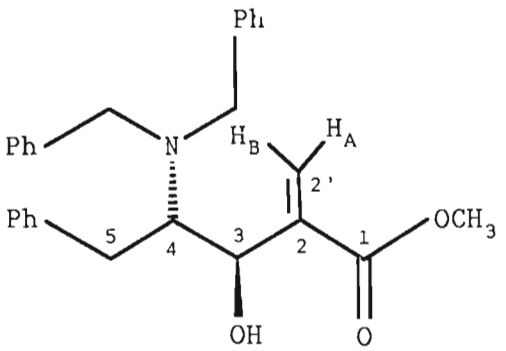
$C_{21}H_{25}NO_3$ (339.44) Calculated: C 74.31 H 7.42 N 4.13
Found (mixture): C 73.9 H 7.47 N 4.21

Methyl 4-(N,N-dibenzylamino)-3-hydroxy-2-methylene-5-phenyl-pentanoate **(216)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(187)** (6.243 g, 18.95 mmol), methyl acrylate (6.83 ml, 75.80 mmol) and DABCO **(56)** (2.126 g, 18.95 mmol), using hexane ethyl acetate (93:7) as eluant, furnished the diastereomeric mixture (6.300 g, **80%**). Repeated recrystallisation afforded the separated major (*anti*) and minor (*syn*) isomers.

$C_{27}H_{29}NO_3$ **MW** 415.54

Major isomer: *anti* **(216 A)**



m.p.: 88-89°C (from hexane-diethyl ether)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

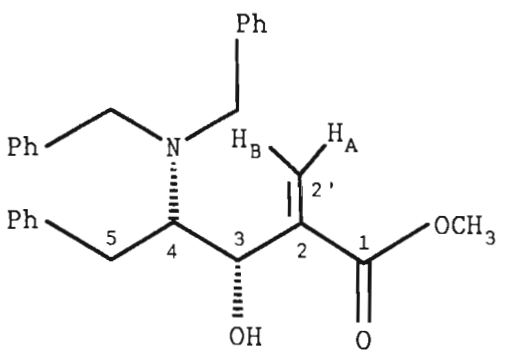
2.68 (1 H, broad m, O*H*)
2.92 and 2.99-3.26 (2 H, AB system, J_{AB} 14.2 Hz, H-5)
2.99-3.26 (1 H, m, H-4)
3.55 (3 H, s, OCH_3)
3.70 (4 H, s, 2 × NCH_2)
4.76 (1 H, d, *J* 5.2 Hz, H-3)
5.77 (1 H, t, *J* 1.1 Hz, H_B)
6.27 (1 H, d, *J* 1.0 Hz, H_A)
7.20 (15 H, m, 2 × $NCH_2C_6H_5$ and C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

31.75 (t, C-5)
51.76 (q, OCH_3)
54.18 (t, NCH_2)
62.49 (d, C-4)
72.67 (d, C-3)

125.74 (d, *C*H aromatics)
126.49 (t, C-2')
126.65, 127.99, 128.15, 128.67, 129.56, (d, *C*H aromatics)
139.69, 141.13 (s, *C*CH_2 aromatics)
141.67 (s, C-2)
166.72 (s, C-1)

Minor isomer: **(216 B)**



m.p.: 84-87°C (from hexane-diethyl ether)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.66 and 3.01-3.27 (2 H, ABX system, J_{AB} 14.1 Hz; J_{AX} 5.9 Hz, H-5)
3.01-3.27 (1 H, m, H-4)
3.52 (3 H, s, O*C*H_3)
3.38 and 3.94 (4 H, AB system, J_{AB} 13.2 Hz, 2 × N*C*H_2)
4.28 (1 H, broad s, O*H*)
4.51 (1 H, m, H-3)
5.69 (1 H, t, *J* 1.1 Hz, H_B)
6.19 (1 H, d, *J* 1.3 Hz, H_A)
7.23 (15 H, m, 2 × $NCH_2C_6H_5$ and $C_6H_5CH_2$)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

32.17 (t, C-5)
51.58 (q, OCH_3)
53.94 (t, NCH_2)
64.47 (d, C-4)
69.79 9d, C-3)
126.22, 127.20 (d, CH aromatics)
127.90 (t, C-2')
128.40, 129.13, 129.35 (d, CH aromatics)
138.94, 139.84 (s, CCH_2 aromatics)
141.33 (s, C-2)
166.63 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.365

m/z (EI):

397(M^+-18, 2), 324(6), 115(3), 91(100), 77(4), 65(9) and 59(1).

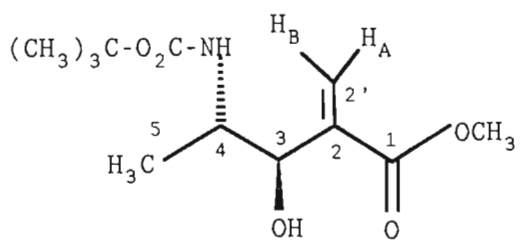
$C_{27}H_{29}NO_3$ (415.54) Calculated: C 78.04 H 7.04 N 3.37
Found (mixture): C 78.10 H 7.06 N 3.33

Methyl 4-{[N(tert-butyloxy)carbonyl]amino}-3-hydroxy-2-methylenepentanoate **(196)**

Application of **GENERAL PROCEDURE 4** to the crude (optically active) aldehyde **(179a)** (4.006 g, 23.13 mmol), methyl acrylate (8.33 ml, 92.52 mmol) and DABCO **(56)** (2.595 g, 23.13 mmol), using hexane-ethyl acetate (96:4) as eluant, furnished the diastereomeric mixture (2.416 g, **76%**).

$C_{12}H_{21}NO_5$ **MW** 259.31

Minor isomer: *anti* **(196 A)**



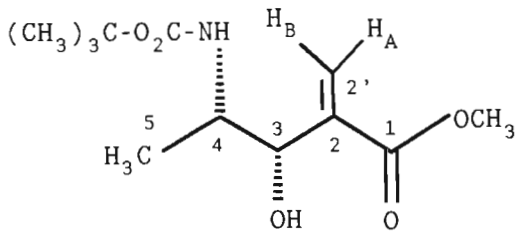
^{1}H n.m.r. (200 MHz; $CDCl_3$) (selected shifts) δ/ppm:

1.08 (3 H, d, *J* 6.8 Hz, H-5)
1.43 (9 H, s, $C[CH_3]_3$)
3.78 (3 H, s, OCH_3)
4.90 (1 H, m, O*H*/N*H*)
5.92 (1 H, m, H_B)
6.34 (1 H, m, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.17 (q, C-5)
28.35 (q, $C[CH_3]_3$)
49.98 (d, C-4)
51.92 (q, OCH_3)
73.54 (d, C-3)
79.36 (s, $C[CH_3]_3$)
127.10 (t, C-2')
139.76 (s, C-2)
156.26 (s, NCO)
166.65 (s, C-1)

Major isomer: *syn* **(196 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.23 (3 H, d, *J* 6.9 Hz, H-5)
1.39 (9 H, s, $C[CH_3]_3$)
3.78 (3 H, s, OCH_3)
3.90 (1 H, m, H-4)
4.44 (1 H, m, H-3)
4.90 (1 H, *OH/NH*)
5.92 (1 H, m, H_B)
6.32 (1 H, m, H_A)

^{13}C n.m.r. (50 MHz;$CDCl_3$) δ/ppm:

18.19 (q, C-5)
28.26 (q, $C[CH_3]_3$)
49.57 (d, C-4)
51.92 (q, OCH_3)
73.65 (d, C-3)
79.44 (s, $C[CH_3]_3$)
126.11 (t, C-2')
140.56 (s, C-2)
156.26 (s, NCO)
166.65 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ $(NHCOCCl_3)_{syn-anti}$ = 0.135

m/z (EI):

186(M^+-73, 7), 144(48), 84(28), 83(31), 116(27), 59(14), 57(100) and 55(13).

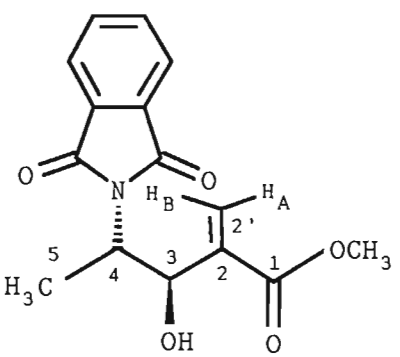
$C_{12}H_{21}O_5$ (259.31) Calculated: C 55.58 H 8.16 N 5.40
Found (mixture): C 55.59 H 7.91 N 5.12

Methyl 4-[(N-phthaloyl)amino]-3-hydroxy-2-methylene-pentanoate **(217)**

Application of **GENERAL PROCEDURE 4** to the crude aldehyde **(188)** (13.49 g, 66.39 mmol), methyl acrylate (23.91 ml, 265.55 mmol) and DABCO **(56)** 7.448 g, 66.39 mmol), using hexane-ethyl acetate (93:7) as eluant, furnished the diastereomeric mixture (3.450 g, **28%**).

$C_{15}H_{15}NO_5$ **MW** 289.29

Minor isomer: *anti* **(217 A)**



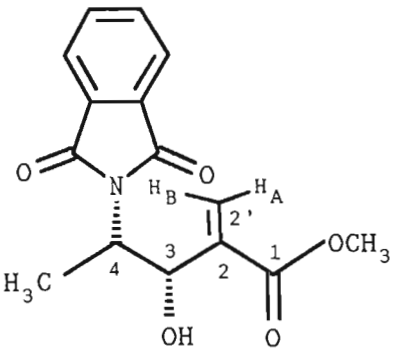
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.52 (3 H, d, *J* 6.9 Hz, H-5)
3.80 (3 H, s, OCH_3)
4.63 (1 H, m, H-4)
4.89 (1 H, m, H-3)
5.34 (1 H, broad s, O*H*)
5.91 (1 H, t, *J* 1.21 Hz, H_B)
6.26 (1 H, t, *J* 1.0 Hz, H_A)
7.79 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.34 (q, C-5)
50.21 (d, C-4)
52.11 (q, OCH_3)
73.50 (d, C-3)
123.52 (d, *C*H aromatics)
126.78 (t, C-2')
131.68 (s, *C*CON aromatics)
134.26 (d, *C*H aromatics)
140.00 (s, C-2)
166.17 (s, C-1)
168.68 (s, N*C*O)

Major isomer: *syn* **(217 B)**



m.p.: 82-84°C (from petroleum ether-CH_2Cl_2-diethyl ether)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.44 (3 H, d, *J* 7.1 Hz, H-5)
3.79 (3 H, s, OCH_3)
4.33 (1 H, d, *J* 5.8 Hz, O*H*)
4.63 (1 H, dq, *J* 7.1 and 5.3 Hz, H-4)
4.87 (1 H, m, H-3)
5.97 (1 H, t, *J* 1.3 Hz, H_B)
6.30 (1 H, dd, *J* 1.3 and 0.8 Hz, H_A)
7.79 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

12.68 (q, C-5)
50.52 (d, C-4)
52.06 (q, OCH_3)
73.09 (d, C-3)
123.41 (d, *C*H aromatics)
127.88 (t, C-2')
131.70 (s, *C*CON aromatics)
134.21 (d, *C*H aromatics)
138.76 (s, C-2)
166.38 (s, C-1)
168.64 (s, N*C*O)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.091

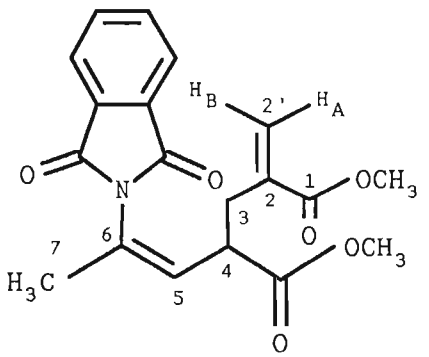
m/z (EI):

258(M^+-31, 1), 160(5), 132(2), 131(3), 115(3), 83(9), 76(12), 59(1) and 56(2).

$C_{15}H_{15}NO_5$ (289.29) Calculated: C 62.28 H 5.23 N 4.84
Found (mixture): C 62.28 H 5.30 N 4.72

Methyl 6-[(N-phthaloyl)amino]-4-carboxymethyl-2-methyl-ene-hept-5-enoate **(223)**

Was isolated (**26%**) by crystallisation (petroleum ether-CH_2Cl_2-diethyl ether) from the crude reaction product **(217)**.



$C_{19}H_{19}NO_6$ **MW** 357.37

m.p.: 127-129°C

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

2.03 (3 H, d, *J* 1.1 Hz, H-7)
2.64 (2 H, m, H-3)

3.35 (1 H, m, H-4)
3.54 (3 H, s, OCH_3)
3.62 (3 H, s, OCH_3)
5.58 (1 H, d, *J* 1.2 Hz, H_B)
5.80 (1 H, m, H-5)
6.18 (1 H, d, *J* 1.3 Hz, H_A)
7.83 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

21.32 (q, C-7)
35.40 (t, C-3)
43.77 (d, C-4)
51.67 (q, OCH_3)
51.96 (q, OCH_3)
123.57 (d, *C*H aromatics)
128.00 (t, C-2')
128.18 (d, C-5)
129.49 (s, *C*CO aromatic)
132.06 (s, C-6)
134.20 (d, *C*H aromatics)
136.45 (s, C-2)
166.66 (s, C-1)
166.73 (s, C-1')
172.83 (s, *C*ON)

m/z (CI;CH_4):

358(MH^+, 32), 356(M^+-1, 3), 326(100), 298(40) and 228(8).

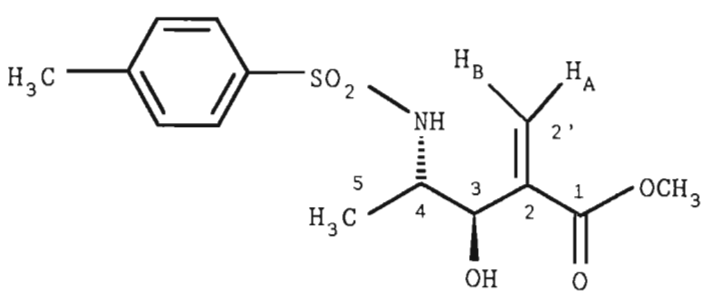
$C_{19}H_{19}NO_6$ (357.37) Calculated: C 63.86 H 5.36 N 3.92
Found: C 63.21 H 5.44 N 3.20

Methyl (3R, 4S) and (3S, 4S) 4-[(N-p-toluenesulfonyl)amino--3-hydroxy-2-methylenepentanoate **(218)**

Application of **GENERAL PROCEDURE 4** to the crude aldehyde **(212)** (5.296 g, 23.30 mmol), methyl acrylate (8.39 mmol) and DABCO **(56)** (2.614 g, 23.30 mmol) afforded the crude product (4.965 g, **68%**). A *sample* was purified for analytical purposes, using hexane-ethyl acetate (70:30, 90:10) as eluant.

$C_{14}H_{19}NO_5S$ **MW** 313.37

Minor isomer: *anti* **(218 A)**



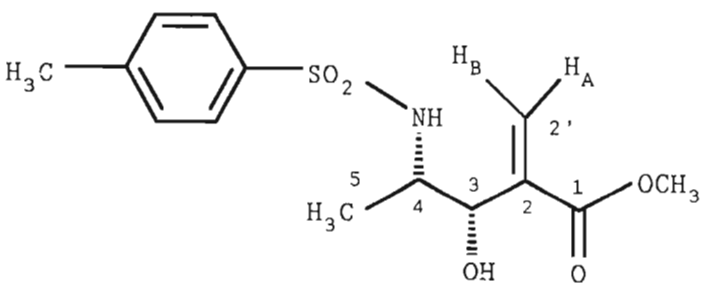
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.92 (3 H, d, *J* 6.9 Hz, H-5)
2.42 (3 H, s, $CH_3C_6H_4$)
3.04 (1 H, m, O*H*)
3.74 (3 H, s, OCH_3)
3.58-3.74 (1 H, m, H-4)
4.49 (1 H, m, H-3)
5.19 (1 H, d, *J* 8.8 Hz, N*H*)
5.91 (1 H, t, *J* 1.3 Hz, H_B)
6.33 (1 H, t, *J* 1.1 Hz, H_A)
7.29 and 7.75 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.12 (q, C-5)
21.54 (q, $CH_3C_6H_4$)
52.04 (q, OCH_3)
52.40 (d, C-4)
72.99 (d, C-3)
127.10 (d, *C*H aromatics)
127.63 (t, C-2')
129.68 (d, *C*H aromatics)
137.84 (s, CCH_3 aromatic)
139.17 (s, CSO_2 aromatic)
143.39 (s, C-2)
166.42 (s, C-1)

Major isomer: *syn* **(218 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.12 (3 H, d, *J* 6.8 Hz, C-5)
2.04 (3 H, s, $CH_3C_6H_4$)
2.92 (1 H, m, O*H*)
3.58-3.74 (1 H, m, H-4)
3.70 (3 H, s, OCH_3)
4.32 (1 H, m, H-3)

5.09 (1 H, d, *J* 8.1 Hz, N*H*)
5.88 (1 H, t, *J* 1.2 Hz, H_B)
6.24 (1 H, t, *J* 1.9 Hz, H_A)
7.29 and 7.75 (4 H, m, C_6H_4)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

19.10 (q, C-5)
21.52 (q, $CH_3C_6H_4$)
51.93 (q, OCH_3)
52.68 (d, C-4)
73.68 (d, C-3)
127.10 (d, CH aromatics)
127.55 (t, C-2')
129.54 (d, CH aromatics)
137.81 (s, CCH_3 aromatic)
138.92 (s, CSO_2 aromatic)
143.19 (s, C-2)
166.37 (s, C-1)

^{1}H n.m..r (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ ($CONH_{syn}$ - $CONH_{anti}$) = 0.280

m/z (EI):

312(M^+-1, 1), 284(10), 158(7), 157(9), 155(69), 91(100), 84(20), 59(7), 56(8) and 55(6).

m/z (CI; CH_4):

314(MH^+, 100), 312(M^+-1, 1), 298(3), 282(44), 198(31), 157(9) and 155(7).

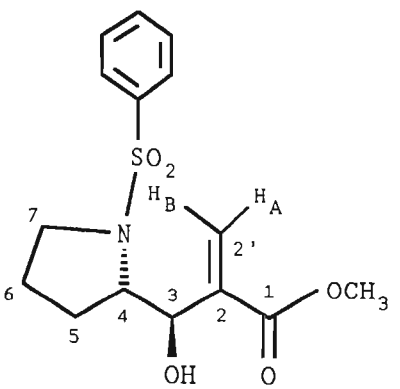
$C_{14}H_{19}NO_5S$ (313.37) Calculated: C 53.66 H 6.11 N 4.47
Found (mixture): C 53.80 H 6.50 N 4.29

Methyl 3-hydroxy-2-methylene-3-[2''(N-benzenesulfonyl)-pyrollidino]propionate **(219)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(204)** (3.733 g, 15.60 mmol), methyl acrylate (5.62 ml) and DABCO **(56)** (1.750 g, 15.60 mmol), using hexane-ethyl acetate (70:30) as eluant, furnished the diastereomeric mixture. Further chromatography, [hexane-ethyl acetate (85:15)], followed by recrystallisation, afforded the pure major (*anti*) diastereomer (2.792 g, 55%) and the relatively *impure* minor (*syn*) isomer.

$C_{15}H_{19}NO_5S$ **MW** 325.38

Major isomer: *anti* **(219 A)**



m.p.: 125-128°C (from hexane-CH_2Cl_2)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.35 (2 H, m, H-6)
1.82 (2 H, m, H-5)
3.12 (1 H, d, *J* 4.8 Hz, O*H*)
3.27-3.55 (2 H, m, H-7)

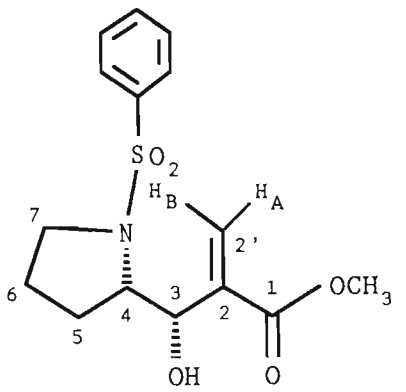
3.82 (3 H, s, CH_3)
3.89 (1 H, m, H-4)
4.97 (1 H, m, H-3)
6.03 (1 H, t, *J* 1.6 Hz, H_B)
6.39 (1 H, t, *J* 1.3 Hz, H_A)
7.51-7.93 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

24.19 (t, C-6)
25.71 (t, C-5)
50.61 (t, C-7)
51.96 (q, CH_3)
62.72 (d, C-4)
71.75 (d, C-3)
127.19 (t, C-2')
127.81, 129.12, 132.92 (d, CH aromatics)
136.49 (s, CSO aromatic)
138.88 (s, C-2)
166.41 (s, C-1)

$C_{15}H_{19}NO_5S$ (325.38) Calculated: C 55.37 H 5.89 N 4.31
Found: C 55.69 H 6.03 N 4.32

Minor isomer: *syn* **(219 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.35 (2 H, m, H-6)
1.82 (2 H, m, H-5)
3.25-3.50 (2 H, m, H-7)
3.81 (3 H, s, CH_3)
3.86 (1 H, d, *J* 4.4 Hz, O*H*)
4.08 (1 H, dt, *J* 7.7 and 3.8 Hz, H-4)
4.42 (1 H, m, H-3)
5.95 (1 H, t, *J* 1.0 Hz, H_B)
6.36 (1 H, d, *J* 1.0 Hz, H_A)
7.52-7.90 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

24.36 (t, C-6)
28.56 (t, C-5)
49.87 (t, C-7)
52.03 (q, CH_3)
64.42 (d, C-4)
74.04 (d, C-3)
127.66 (d, CH aromatics)
128.02 (t, C-2')

129.25, 133.06 (d, CH aromatics)
137.07 (s, CSO aromatic)
140.16 (s, C-2)
166.77 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.159

m/z (EI):

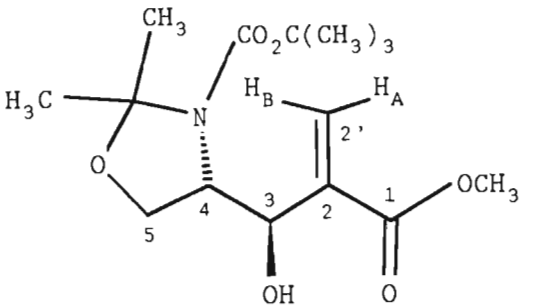
294(M^+-31, 2), 210(100), 141(14), 77(14) and 55(1).

Methyl 3-hydroxy-3-[4-(1',1'-dimethylethyl 2'',2''-dimethyl-3'-oxazolidinecarboxylate)]-2-methylenepropanoate **(220)**

Application of **GENERAL PROCEDURE 4** to the aldehyde **(175)** (0.702 g, 3.06 mmol), methyl acrylate (1.10 ml, 12.24 mmol) and DABCO **(56)** (0.343 g, 3.06 mmol), using hexane-ethyl acetate (96:4) as eluant, furnished the diastereomeric mixture (0.415 g, **43%**).

$C_{15}H_{25}NO_6$ **MW** 315.37

Major isomer: *anti* **(220 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

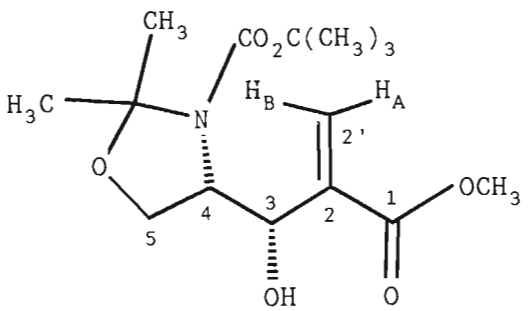
1.45 (9 H, s, $C[CH_3]_3$)
1.43 (3 H, s, CH_3CN)
1.52 (3 H, s, CH_3CN)
3.80 (3 H, s, OCH_3)
3.91 (1 H, m, H-4 or H-3/H-5/O*H*)
4.19 (2 H, m, H-5 or H-3/H-4/O*H*)
4.52 (2 H, m, H-3 or H-4/H-5/O*H*)
5.83 (1 H, m, H_B)
6.29 (1 H, m, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

23.96 (q, CH_3CN)
26.94 (q, CH_3CN)
28.26 (q, $C[CH_3]_3$)
51.84 (q, OCH_3)
61.61 (d, C-4)
64.86 (t, C-5)
73.96 (d, C-3)
80.77 (s, $C[CH_3]_3$)
94.08 (s, $OC[CH_3]_2N$)
126.66 (t, C-2')
139.69 (s, C-2)
153.67 (s, NCOO)

167.01 (C-1)

Minor isomer: *anti* **(220 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.49 (9 H, s, $C[CH_3]_3$)
1.40-1.65 (6 H, s, 2 × CH_3CN)
3.79 (3 H, s, OCH_3)
3.91 (1 H, m, H-4 or H-3/H-5/O*H*)
4.19 (2 H, m, H-5 or H-3/H-4/O*H*)
4.52 (2 H, m, H-3 or H-4/H-5/O*H*)
5.83 (1 H, m, H_B)
6.29 (1 H, m, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

22.88 (q, CH_3CN)
27.31 (q, CH_3CN)
28.65 (q, $C[CH_3]_3$)
51.94 (q, OCH_3)
59.81 (d, C-4)
63.86 (t, C-5)
72.06 (d, C-3)

80.64 (s, $C[CH_3]_3$)
94.11 (s, $OC[CH_3]_2N$)
127.84 (t, C-2')
139.20 (s, C-2)
153.63 (s, NCOO)
167.01 (C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.095

m/z (EI):

300(M^+-15, 0.1), 242(1.7), 116(21.9), 115(23.8), 101(5.9), 100(85.5), 86(2.8), 85(2.8), 84(18.7), 73(0.4), 59(5.7), 57(100) and 43(4.9).

$C_{15}H_{25}NO_6$ (315.37) Calculated: C 57.13 H 7.99 N 4.44
Found (mixture): C 56.88 H 8.12 N 4.38

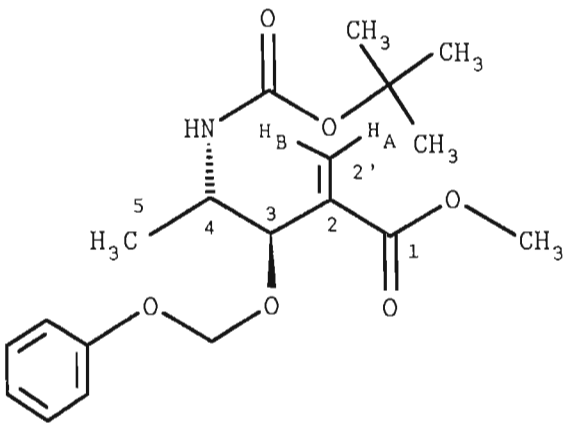
5.2.12 BOM-PROTECTION OF THE γ-AMINO ALCOHOL.

Methyl 4-{[N(tert-butyloxy)carbonyl]amino}-3-[(benzyloxy)-methoxy]-2-methylenepentanoate **(237)**

Application of **GENERAL PROCEDURE 1(B)** to the crude diastereomeric mixture **(196)** (1.0 g, 3.86 mmol), (reaction time: ≥ *7 days*), using hexane-ethyl acetate as eluant, afforded the title compound (0.59 g, **44%**).

$C_{20}H_{29}NO_5$ **MW** 363.46

Minor isomer: *anti* **(237 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

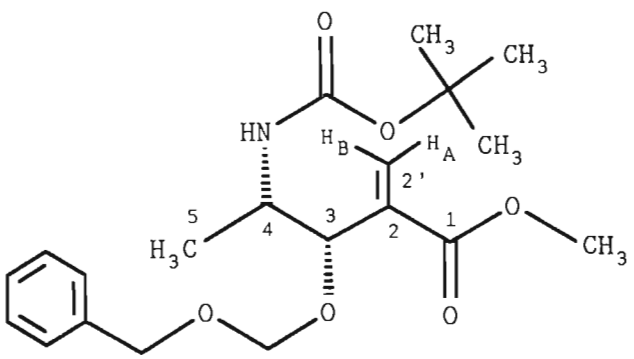
1.08 (3 H, d, *J* 6.8 Hz, H-5)
1.38 (9 H, s, $C[CH_3]_3$)
3.77 (3 H, s, OCH_3)
4.00 (1 H, broad s, N*H*)
4.51-4.78 (6 H, m, H-3; H-4; OCH_2O and CH_2Ph)
5.90 (1 H, broad s, H_B)
6.42 (1 H, dd, *J* 1.4 and 0.6 Hz, H_A)
7.33 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

15.39 (q, C-5)
28.29 (q, $C[CH_3]_3$)
48.59 (d, C-4)
52.04 (q, OCH_3)
70.22 (t, CH_2Ph)
77.59 (d, C-3)
93.55 (t, OCH_2O)
127.28 (t, C-2')
127.79, 127.83, 128.47 (d, CH aromatics)

138.03 (s, C-2)
155.48 (s, NCO)
166.15 (s, C-1)

Major isomer: *syn* **(237 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.27 (3 H, d, *J* 6.9 Hz, H-5)
1.39 (9 H, s, $C[CH_3]_3$)
3.77 (3 H, s, OCH_3)
4.00 (1 H, broad s, N*H*)
4.51-4.78 (6 H, m, H-3; H-4; OCH_2O and CH_2Ph)
5.84 (1 H, broad s, H_B)
6.36 (1 H, broad s, H_A)
7.33 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

18.91 (q, C-5)
28.39 (q, $C[CH_3]_3$)
48.72 (d, C-4)
51.95 (q, OCH_3)
70.13 (t, CH_2Ph)

76.62 (d, C-3)
92.96 (t, OCH_2O)
126.26 (t, C-2')
127.79, 127.83, 128.47 (d, CH aromatics)
137.43 (s, CCH_2 aromatic)
138.47 (s, C-2)
155.48 (s, NCO)
166.15 (s, C-1)

m/z (EI):

262(M^+-101, 1), 205(1), 178(2), 144(12), 121(1), 120(2), 116(1), 115(16), 107(1), 100(1), 91(100), 77(2), 65(6), 59(14), 57(47), 55(2), 44(27), 42(1) and 41(4).

$C_{20}H_{29}NO_5$ (363.46) Calculated: C 66.09 H 8.04 N 3.86
Found: No satisfactory analysis.

5.2.13. THE CHIRAL ACRYLIC ESTERS.

GENERAL PROCEDURE 9:

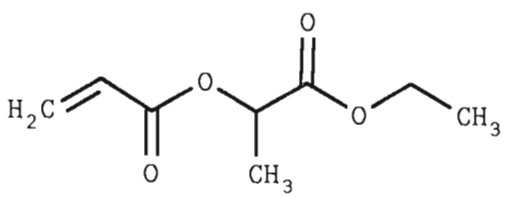
Preparation of the chiral acrylates.

Acryloyl chloride (1 equivalent) was added dropwise to a stirred solution of triethylamine (1 equivalent) and the chiral alcohol (1 equivalent) in anhydrous dichloromethane (4 ml/mmol alcohol) at 0°C. The resulting mixture was stirred for 4 h. at 0°C, then allowed to attain room temperature. The mixture was extracted with dilute (1 M) hydrochloric acid (40 ml/30 mmol Et_3N) and a saturated solution of sodium hydrogen carbonate. The organic layer was

dried and concentrated under reduced pressure to afford the crude acrylate.

(S)-(-)-1-Methyl ethylethanoyl acrylate **(79)**

Application of **GENERAL PROCEDURE 9** to (S)-(-)-ethyl lactate **(87a)** (3.50 g, 29.63 mmol) afforded the title compound (2.24 g, **44%**) after purification by distillation.



$C_8H_{12}O_4$ **MW** 172.18

b.p.: 39-40°C/0.4 mm Hg.

[α]$_D^{22.9}$: -37.96° (*c* 0.22, $CHCl_3$) [Lit.,[86] [α]$_D^{22}$ -37.1° (*c* 2.7, $CHCl_3$).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.28 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.54 (3 H, d, *J* 7.1 Hz, CH_3CH)
4.22 (2 H, q, *J* 7.1 Hz, CH_2CH_3)
5.15 (1 H, q, *J* 7.1 Hz, $CHCH_3$)
5.87-6.54 (3 H, m, CH_2=CH)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm;

14.10 (q, CH_3CH_2)

16.98 (q, CH_3CH)
61.41 (t, OCH_2)
68.81 (d, OCH)
127.71 (d, $CH=CH_2$)
131.83 (t, $CH_2=CH$)
165.44 (s, $COCH=CH_2$)
170.73 (s, $COOCH_2$)

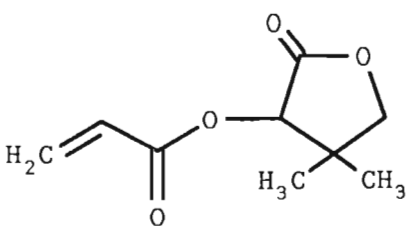
m/z (EI):

172(M^+, 1), 127(18), 126(1), 99(61), 55(100) and 45(3).

$C_8H_{12}O_4$ (172.18) Calculated: C 55.81 H 7.03
Found: C 55.62 H 7.12

(R)-(+)-Pantolactone acrylate **(78)**

Application of **GENERAL PROCEDURE 9** to (R)-(-)-pantolactone (3.86 g, 29.66 mmol) afforded the title compound (4.40 g, **74%**) after purification by distillation.



$C_9H_{12}O_4$ **MW** 184.19

b.p.: 144-145°C/4.0 mm Hg (Lit.,[123] 84°C/0.1 mm Hg).

$[\alpha]_D^{25.5}$: +6.48° (*c* 3.23, CH_2Cl_2) [Lit.,[123] $[\alpha]_D^{20}$ +6.5° (*c* 17, CH_2Cl_2).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.14 (3 H, s, CH_3)
1.23 (3 H, s, CH_3)
4.09 (2 H, s, OCH_2)
5.47 (1 H, s, OCH)
5.96-6.59 (3 H, m, CH_2=CH)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

19.91 (q, CH_3)
22.99 (q, CH_3)
40.47 (s, $C[CH_3]_2$)
75.37 (d, OCH)
76.43 (t, OCH_2)
127.40 (d, $CH=CH_2$)
133.26 (t, CH_2=CH)
165.30 (s, $COCH=CH_2$)
172.92 (s, $COOCH_2$)

m/z (EI):

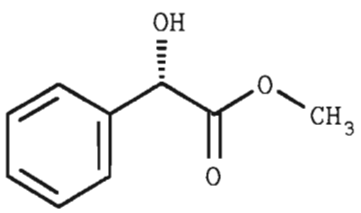
184(M^+, 1), 84(1), 83(2), 82(1), 70(1), 69(1), 68(2), 67(1), 57(3), 55(100), 42(1) and 41(4).

$C_9H_{12}O_4$ (184.19) Calculated: C 58.69 H 6.57
Found: C 58.39 H 6.57

(R)-(-)-Methyl mandelate **(96a)**

A stirred mixture of (R)-(-) mandelic acid (5.0 g, 32.86 mmol) and a catalytic amount of *conc.* H_2SO_4 was refluxed for

3.5 h. The cooled reaction mixture was taken up in chloroform and washed with 2 N $NaHCO_3$ and water. The organic layer was dried and concentrated under reduced pressure to afford the crude ester (4.77 g, **87%**), which was used without further purification.



$C_9H_{10}O_3$ **MW** 166.18

m.p.: 53-55°C (Lit.,[216] 56-58°C).

^{1}H n.m.r. (80 MHz; $CDCl_3$) δ/ppm:

3.61 (1 H, broad s, O*H*)
3.70 (3 H, s, C*H*$_3$)
5.11 (1 H, m, C*H*OH)
7.30 (5 H, m, C$_6$*H*$_5$)

^{13}C n.m.r. (20 MHz; $CDCl_3$) δ/ppm;

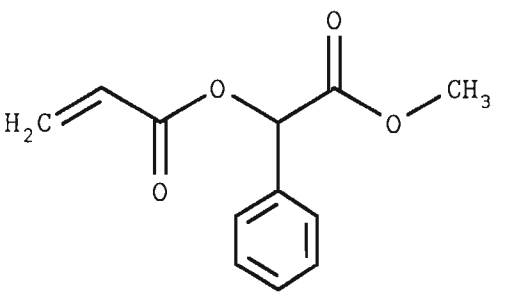
52.58 (q, CH_3O)
72.71 (d, *C*HOH)
126.46, 128.22, 128.38 (d, *C*H aromatics)
138.29 (s, *C*CH aromatic)
173.85 (s, *C*OO)

m/z (EI):

166(M^+, 45), 107(100), 106(3), 105(8) and 77(22).

(R)-(-)-1-Phenyl methylethanoyl acrylate **(80)**

Application of **GENERAL PROCEDURE** 9 to (R)-(-)-methyl mandelate **(96a)** (4.92 g, mmol) afforded the title compound (4.69 g, **72%**) after purification by flash chromatography, using hexane-ethyl acetate (85:15) as eluant.



$C_{12}H_{12}O_4$ **MW** 220.23

$[\alpha]_D^{25.0}$: -142.41° (*c* 0.45, $CHCl_3$) [Lit.,[86] $[\alpha]_D^{25}$ -133° (*c* 1.5, $CHCl_3$)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

3.69 (3 H, s, CH_3)
5.87-6.57 (3 H, m, CH_2=CH)
6.01 (1 H, s, OCH)
7.44 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

52.75 (q, CH_3)
74.73 (d, OCH)
127.82 (d, CH=CH_2)
128.04, 129.22, 129.71 (d, CH aromatics)
132.75 (t, CH_2=CH)
134.15 (s, CCH aromatic)

166.77 (s, COOCH)
169.67 (s, $COOCH_3$)

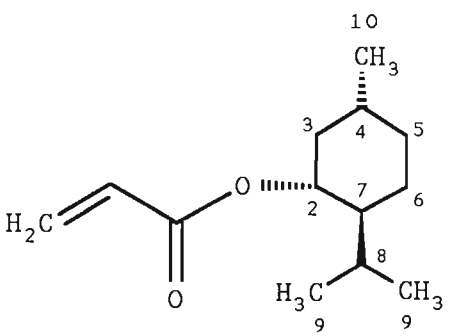
m/z (EI):

220(M^+, 4), 189(2), 188(14), 161(29), 149(1), 118(2), 90(5), 89(5), 77(15) and 55(100).

$C_{12}H_{12}O_4$ (220.23) Calculated: C 65.45 H 5.49
Found: C 65.78 H 5.31

(2R, 4R, 7S)-(-)-Menthyl acrylate **(151a)**

Was available in the research group.



$C_{13}H_{22}O_2$ **MW** 210.32

b.p.: Not determined. (Lit.,[217] 78-80/5 mm Hg).

$[\alpha]_D^{25}$: -86.41° (*c* 0.90, dioxane) [Lit.,[217] $[\alpha]_D^{28}$ -80.2° (*c* 10.02, dioxane)].

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.77 (3 H, d, *J* 6.9 Hz, H-10)
0.85 (1 H, m, H-8)
0.90 (3 H, d, *J* 7.1 Hz, H-9)
0.91 (3 H, d, *J* 6.5 Hz, H-9)
1.07 (2 H, m, H-5)
1.45 (2 H, m, H-6)
1.69 (2 H, m, H-3)
1.91 (1 H, m, H-4)
2.04 (1 H, m, H-7)
4.77 (1 H, dt, *J* 10.8 and 4.4 Hz, H-2)
5.77-6.44 (3 H, m, CH_2=CHCOO)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

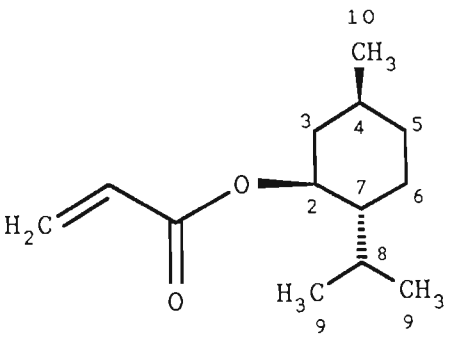
16.42 (q, C-10)
20.72 (q, C-9)
22.03 (q, C-9)
23.54 (t, C-5)
26.33 (d, C-8)
31.39 (d, C-4)
34.27 (t, C-6)
40.87 (t, C-3)
47.09 (d, C-7)
74.32 (d, C-2)
129.03 (d, CH_2=CHCO)
130.20 (t, CH_2=CHCO)
165.83 (s, COO)

m/z (EI):

210(M^+, 0.03), 195(0.17), 167(0.53), 125(2.51), 110(5.86), 109(9.47), 97(7.10), 96(22.55), 84(2.01), 83(16.27), 82(24.69), 81(67.40), 71(4.80), 70(4.28), 56(11.85), 55(100) and 43(46.83).

(2S, 4S, 7R)-(+)-Menthyl acrylate **(151b)**

Was available in the research group.



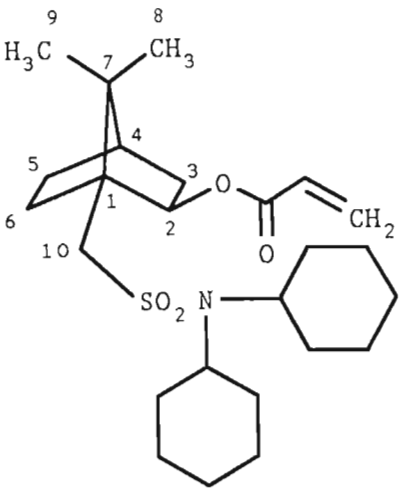
$[\alpha]_D$: +82.05° (*c* 0.40, dioxane)

^{1}H n.m..r.: As for **(151a)**

^{13}C n.m.r.: As for **(151a)**

(1R, 2S, 4S)-(-)-1-(Dicyclohexylaminosulfonyl)-methyl-7,7-dimethylbicyclo[2.2.1]hept-2-yl acrylate **(81b)**

Was available in the research group.



$C_{25}H_{42}NO_4S$ **MW** 452.68

m.p.: 200-203°C (Lit.,[88a] 198-199° C).

$[\alpha]_D$: +32.68° (*c* 0.41, absolute EtOH)

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.90 (3 H, s, H-9/H-8)
1.02 (3 H, s, H-8/H-9
1.09-1.33 (7 H, m)
1.56-1.78 (19 H, m)
1.93-2.07 (2 H, m)
2.69 and 3.27 (2 H, AB system, J_{AB} 13.3 Hz, H-10)
3.23 (2 H, m, 2 × NC*H*)
5.10 (1 H, m, H-2)
5.78-6.41 (3 H, m, C*H*=CH_2)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

20.02 (q, C-9/C-8)
20.46 (q, C-8/C-9)
25.13, 26.42, 27.01, 29.91, 32.75, 39.39 (t, C-3, C-5, C-6 and cyclohexyl CH_2)

44.50 (d, C-4)
49.12 (s, C-7)
49.48 (s, C-1)
53.63 (t, C-10)
57.39 (d, NCH)
78.38 (d, C-2)
129.14 (d, $CH=CH_2$)
129.87 (t, $CH_2=CH$)
164.50 (s, COO)

m/z (EI):

452(M^+, 0.4), 451(4.2), 244(30.8), 180(29.50), 179(11.8), 99(2.1), 98(17.1), 96(6.0), 83(24.3), 82(8.4), 81(14.7) and 55(100).

5.2.14 THE (CHIRAL ESTER-BENZALDEHYDE) CONDENSATION PRODUCTS.

GENERAL PROCEDURE 10:

Reaction of the chiral esters with benzaldehyde.

Benzaldehyde (4.00 g, 37.69 mmol) was added, neat, to a stirred mixture of the chiral acrylate (18.85 mmol) and DABCO **(56)** (2.115 g, 18.85 mmol) at ambient temperature. The reactions were stoppered and stirred for approximately 2 weeks, (see TABLE 29). The reaction mixture was diluted with dichloromethane, (or chloroform), and washed sequentially with dilute (2 N) hydrochloric acid and water. The organic layer was dried and concentrated under reduced pressure to

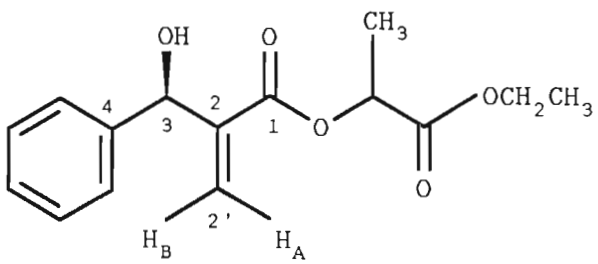
afford the crude product. Ratio analysis, (see TABLE 29), was carried out directly on the mixture, by ^1H n.m.r. Subsequent purification by flash chromatography afforded the pure diastereomeric mixture.

(S)-(-)-Ethyl lactate ester of (3S) and (3R) [(3-hydroxy-2-methylene-3-phenyl)propanoic acid] **(245)**

Application of **GENERAL PROCEDURE 10**, using the chiral ester **(79)** (3.24 g, 18.85 mmol), and hexane-ethyl acetate (90:10; 70:30) as eluant, afforded the title compound.

$C_{15}H_{18}O_5$ **MW** 278.31

Major isomer: *(3S)* **(245 A)**



^1H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

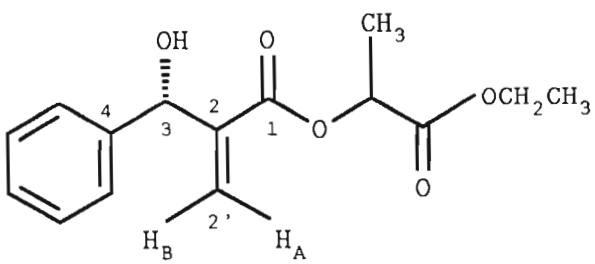
1.17 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.43 (3 H, d, *J* 7.1 Hz, CH_3CH)
3.36 (1 H, broad s, OH)
4.14 (2 H, q, *J* 7.1 Hz, CH_2CH_3)
5.07 (1 H, q, *J* 7.3 Hz, $CHCH_3$)
5.55 (1 H, s, H-3)
5.96 (1 H, t, *J* 1.2 Hz, H_B)
6.43 (1 H, t, *J* 0.9 Hz, H_A)

7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.98 (q, CH_3CH_2)
16.81 (q, CH_3CH)
61.47 (t, OCH_2)
68.98 (d, $CHCH_3$)
72.91 (d, C-3)
126.98 (d, CH aromatics)
127.33 (t, C-2')
128.08, 128.70 (d, CH aromatics)
141.42 (s, C-4 aromatic)
141.87 (s, C-2)
165.31 (s, C-1)
170.64 (s, COOEt)

Minor isomer: *(3R)* **(245 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.17 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.45 (3 H, d, *J* 7.1 Hz, CH_3CH)
3.36 (1 H, broad s, OH)
4.13 (2 H, q, *J* 7.0 Hz, OCH_2)
5.07 (1 H, q, *J* 7.3 Hz, $CHCH_3$)

5.59 (1 H, s, H-3)
5.80 (1 H, t, *J* 1.2 Hz, H_B)
6.46 (1 H, t, *J* 0.9 Hz, H_A)
7.31 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.98 (q, CH_3CH_2)
16.81 (q, CH_3CH)
61.52 (t, OCH_2)
68.98 (d, $CHCH_3$)
72.64 (d, H-3)
127.24 (t, C-2')
127.24, 128.19, 128.72 (d, CH aromatics)
141.02 (s, C-4 aromatic)
141.52 (s, C-2)
165.48 (s, C-1)
170.57 (s, COOEt)

m/z (EI):

278(M^+, 1), 233(1), 161(12), 160(38), 159(7), 133(17), 132(100), 117(23), 116(12), 115(38), 107(16), 106(5), 104(45), 89(4), 77(35), 65(1), 45(3) and 43(3).

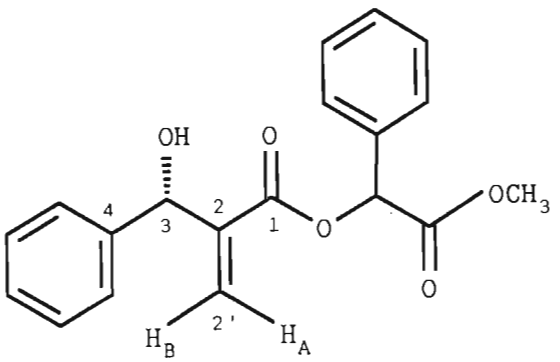
$C_{15}H_{18}O_5$ (278.31) Calculated: C 64.74 H 6.52
Found (mixture): C 64.67 H 6.72

(R)-(-)-Methyl mandelate ester of (3R) and (3S) [(3-hydroxy-2-methylene-3-phenyl)propanoic acid] **(246)**

Application of **GENERAL PROCEDURE 10**, using the chiral ester **(80)** (4.147 g, 18.85 mmol), and hexane-ethyl acetate (85;15) as eluant, afforded the title compound.

$C_{19}H_{18}O_5$ **MW** 326.35

Major isomer: *(3R)* **(246 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

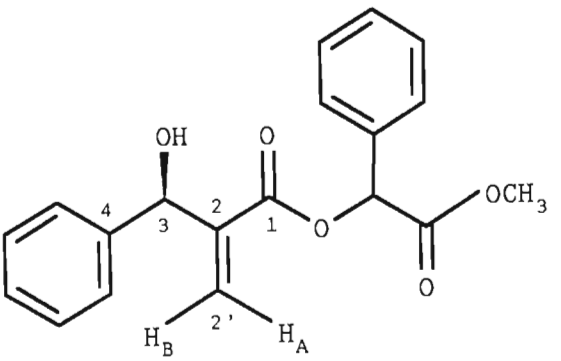
3.24 (1 H, m, O*H*)
3.59 (3 H, s, CH_3)
5.54 (1 H, d, *J* 5.5 Hz, H-3)
5.89 (1 H, s, COOC*H*)
6.01 (1 H, t, *J* 1.1 Hz, H_B)
6.54 (1 H, t, *J* 0.9 Hz, H_A)
7.27 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

52.68 (q, CH_3)
72.96 (d, C-3)
74.53 (d, COO*C*H)
126.63-129.29 (d, *C*H aromatics)
127.94 (t, C-2')
141.23, 140.84 (s, *C*CH aromatic)
141.31 (s, C-2)
165.08 (s, C-1)

169.05 (s, COOMe)

Minor isomer: *(3S)* **(246 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$):

3.24 (1 H, m, O*H*)
3.60 (3 H, s, CH_3)
5.59 (1 H, d, *J* 4.6 Hz, H-3)
5.83 (1 H, s, COOC*H*)
5.93 (1 H, s, H_B)
6.50 (1 H, t, *J* 0.8 Hz, H_A)
7.27 (10 H, m, 2 × C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

52.68 (q, CH_3)
72.68 (d, C-3)
74.58 (d, COOCH)
126.63-129.29 (d, CH aromatics)
140.84, 141.62 (s, CCH aromatics)
127.94 (t, C-2)
165.31 (s, C-1)
169.09 (s, COOMe)

m/z (EI):

177(M^+-149, 37), 161(17), 160(13), 149(13), 133(27), 132(21), 116(26), 115(80), 107(32), 106(13), 105(100), 90(15), 89(16), 77(960, 65(4), 59(7) and 55(13).

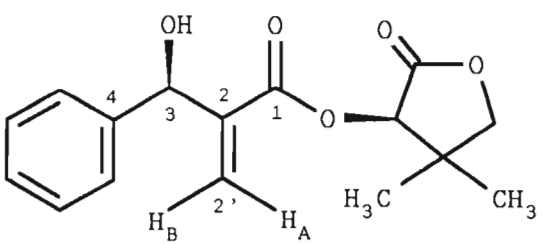
$C_{19}H_{18}O_5$ (326.35) Calculated: C 69.93 H 5.56
Found: No satisfactory analysis.

(R)-(-)-Pantolactone ester of (3S) and (3R) [(3-hydroxy-2-methylene-3-phenyl)propanoic acid] **(247)**

Application of **GENERAL PROCEDURE 10**, using the chiral ester **(78)** (3.468 g, 18.85 mmol), and hexane-ethyl acetate (85:15; 75:25) as eluant, afforded the title compound.

$C_{16}H_{18}O_5$ **MW** 290.32

Major isomer: *(3S)* **(247 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

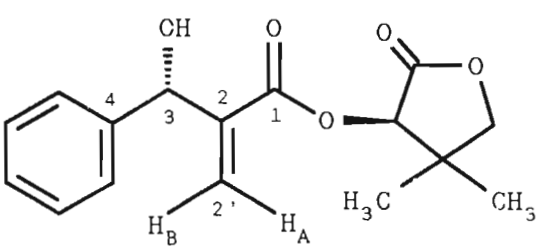
0.88 (3 H, s, CH_3)
1.06 (3 H, s, CH_3)
3.03 (1 H, m, OH)
3.97 (2 H, s, OCH_2)
5.33 (1 H, s, COOCH)

5.58 (1 H, m, H-3)
6.02 (1 H, t, *J* 1.2 Hz, H_B)
6.52 (1 H, t, *J* 1.0 Hz, H_A)
7.32 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

19.59 (q, CH_3)
22.80 (q, CH_3)
40.34 (s, $C[CH_3]_2$)
72.52 (d, C-3)
75.45 (d, COOCH)
76.19 (t, OCH_2)
126.99, 128.12, 128.56 (d, CH aromatics)
128.02 (t, C-2)
140.86 (s, C-4 aromatic)
141.16 (s, C-2)
164.71 (s, C-1)
172.28 (s, $COOCH_2$)

Minor isomer: *(3R)* **(247 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.91 (3 H, s, CH_3)
1.09 (3 H, s, CH_3)

3.12 (1 H, m, O*H*)
3.99 (2 H, s, OCH_2)
5.32 (1 H, s, COOC*H*)
5.58 (1 H, m, H-3)
6.02 (1 H, t, *J* 1.2 Hz, H_B)
6.47 (1 H, t, *J* 0.7 Hz, H_A)
7.32 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

19.64 (q, CH_3)
22.85 (q, CH_3)
40.34 (s, $C[CH_3]_2$)
73.03 (d, C-3)
75.45 (d, COOCH)
76.19 (t, OCH_2)
126.39, 127.85 (d, CH aromatics
127.89 (t, C-2')
128.45 (d, CH aromatic)
140.86 (s, C-4 aromatic)
141.03 (s, C-2)
164.89 (s, C-1)
172.28 (s, $COOCH_2$)

m/z (EI):

290(M^+, 3), 177(20), 161(15), 160(43), 159(33), 133(20), 132(100), 114(12), 113(8), 107(18), 106(7), 105(73), 104(8), 99(70) and 55(3).

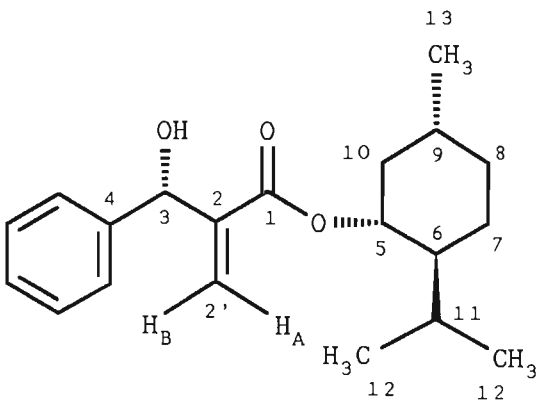
$C_{16}H_{18}O_5$ (290.32) Calculated: C 66.20 H 6.25
Found (mixture): C 66.52 H 6.42

(R)-(-)-Menthol ester of (3R) and (3S) [(3-hydroxy-2-methylene-3-phenyl)propanoic acid] **(248)**

Application of **GENERAL PROCEDURE 10**, using (-)-menthyl acrylate **(151a)** (3.959 g, 18.85 mmol), afforded the crude product as a solid. Subsequent purification by recrystallisation (hexane-CH_2Cl_2) afforded the diastereomeric mixture enriched in the *major* isomer.

$C_{20}H_{28}O_3$ **MW** 316.44

Major isomer: *(3R)* **(248 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

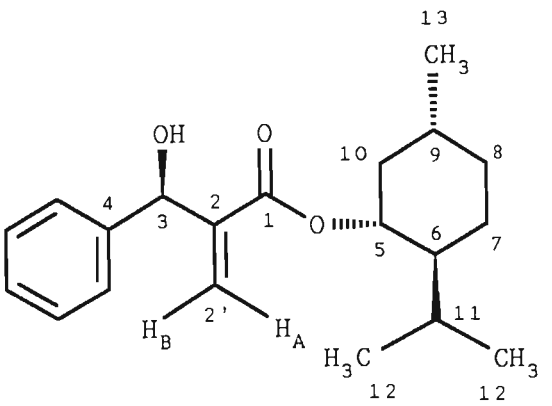
0.61 (3 H, d, *J* 6.9 Hz, H-13)
0.77 (3 H, d, *J* 7.0 Hz, H-12)
0.82 (1 H, m, H-11)
0.88 (3 H, d, *J* 6.5 Hz, H-12)
0.89 (2 H, m, H-8)
1.29 (1 H, m, H-7)
1.43 (2 H, m, H-7 and H-10)
1.61 (2 H, m, H-10 and H-9)
1.91 (1 H, m, H-6)
3.07 (1 H, broad s, O*H*)

4.71 (1 H, dt, *J* 10.9 and 4.4 Hz, H-5)
5.53 (1 H, s, H-3)
5.83 (1 H, t, *J* 1.3 Hz, H_B)
6.33 (1 H, dd, *J* 1.2 and 0.8 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

16.05 (q, C-13)
20.79 (q, C-12)
21.98 (q, C-12)
23.24 (t, C-8)
25.98 (d, C-11)
31.38 (d, C-9)
34.15 (t, C-7)
40.71 (t, C-10)
47.04 (d, C-6)
73.48 (d, C-3)
74.90 (d, C-5)
125.59 (t, C-2')
126.61, 127.78, 128.41 (d, CH aromatics)
141.38 (s, C-4 aromatic)
142.35 (s, C-2)
166.00 (s, C-1)

Minor isomer: *(3S)* **(248 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

Not assigned.

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

Not assigned.

m/z (EI):

177(M^+-139, 55), 161(6), 160(27), 159(23), 139(9), 138(10), 123(11), 109(3), 96(7), 95(41), 94(5), 83(100), 81(38), 79(53), 71(5), 69(33), 55(36) and 43(14).

$C_{20}H_{28}O_3$ (316.44) Calculated: C 75.91 H 8.92
Found (mixture): C 75.68 H 8.97

5.2.15 HYDROLYSIS OF THE (CHIRAL ESTER-BENZALDEHYDE) PRODUCTS.

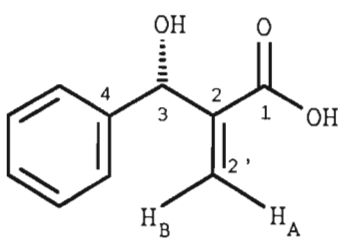
GENERAL PROCEDURE 11:

Hydrolysis of the benzaldehyde-chiral acrylate coupled products.

A mixture of potassium hydroxide (excess) water and the ester were refluxed overnight, (or until t.l.c. indicated consumption of the starting ester). The cooled reaction mixture was concentrated under reduced pressure and unreacted ester was extracted with diethl ether. Acidification of the aqueous phase to pH ~2, followed by extraction with diethyl ether, afforded the crude acid, as an *enantiomerically enriched* mixture, which was purified by flash chromatography, using dichloromethane-methanol (95:5) as eluant.

(3R)-3-Hydroxy-2-methylene-3-phenylpropanoic acid **(250a)**

Application of **GENERAL PROCEDURE 11** to the diastereomeric mixture **(246)**) (0.60 g, 1.84 mmol) in KOH (0.49 g, 8.74 mmol) and water (6.2 ml), afforded the title compound (0.070 g, **21%**), enriched in the *(3R)*-enantiomer.



$C_{10}H_9O_3$ **MW** 177.18

m.p.: Not determined (Lit.,[200] 78-79°C, for the racemic acid).

^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

5.54 (1 H, s, H-3)
5.94 (1 H, t, *J* 1.1 Hz, H_B)
6.47 (1 H, s, H_A)
6.65 (2 H, broad s, O*H*/COO*H*)
7.26-7.38 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

72.82 (d, C-3)
126.63, 127.99, 128.50 (d, CH aromatics)
130.16 (t, C-2')
140.86 (s, C-4)
141.32 (s, C-2)
171.07 (s, C-1)

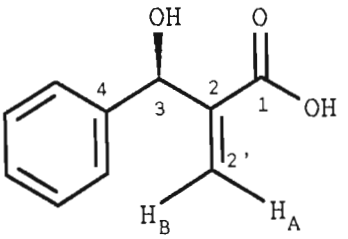
m/z (EI):

177(M^+, 45), 160(17), 159(6), 132(53), 131(18), 107(26), 106(13), 105(100), 101(2), 100(2), 77(75), 71(1), 45(7) and 44(1).

Application of **GENERAL PROCEDURE 11** to the diastereomeric mixture **(248)** (1.00 g, 3.17 mmol) in KOH (3.09 g, 55 mmol) and water (5.5 ml), (reaction time: *7 d*), afforded the title compound (0.10 g, **18%**), enriched in the *(3R)* enantiomer.

Spectral data as for **(250a)**.

(3S)-3-Hydroxy-2-methylene-3-phenylpropanoic acid **(250b)**



Application of **GENERAL PROCEDURE 11** to the diastereomeric mixture **(245)** (0.700 g, 2.52 mmol) in KOH (0.366 g, 5.99 mmol) in water (4.2 ml), (reaction time: *2 d*), afforded the title compound (0.105 g, **23%**), enriched in the *(3S)*-enantiomer.

Spectral data as for **(250a)**.

5.2.16 THE (ALKOXY ALDEHYDE-CHIRAL ESTER) CONDENSATION PRODUCTS.

GENERAL PROCEDURE 12:

Reactions of the chiral alkoxy aldehyde with the chiral esters.

The chiral aldehyde **(104)** (1 equivalent) was added, neat, to a stirred mixture of the chiral acrylate (1 equivalent) and catalyst (0.1-1.0 equivalent), (see TABLE 31). In those cases where molar equivalents of catalyst were employed, a few drops of methanol was added to promote homogeneity of the reaction mixture. The reactions were stoppered and stirred at ambient temperature until ^{1}H n.m.r. indicated consumption of the aldehyde. The reaction mixture was

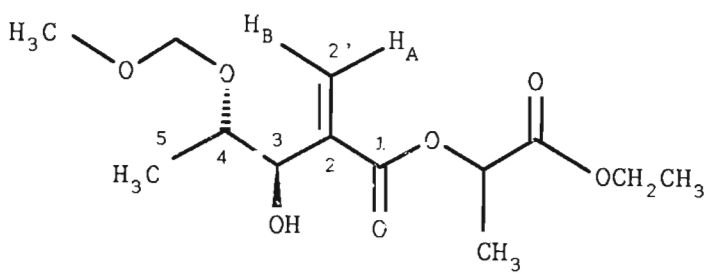
diluted with dichloromethane, (or chloroform), and sequentially washed with dilute (2 N) hydrochloric acid and water. The organic phase was dried and concentrated under reduced pressure to afforded the crude product. Ratio analysis, by ^{1}H n.m.r., was carried out directly on the diastereomeric mixture. Subsequent purification by flash chromatography afforded the pure diastereomeric mixture.

(S)-(-)-Ethyl lactate ester of [(3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoic acid] **(251)**

Application of **GENERAL PROCEDURE 12** to the aldehyde **(104)** (0.45 g, 3.81 mmol), ester **(79)** (0.655 g, 3.81 mmol) and DABCO **(56)** (0.086 g, 0.762 mmol), using hexane-ethyl acetate (70:30) as eluant, afforded the title compound (0.324 g, **29%**).

$C_{13}H_{22}O_7$ **MW** 290.32

Major isomer: *anti* **(251 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

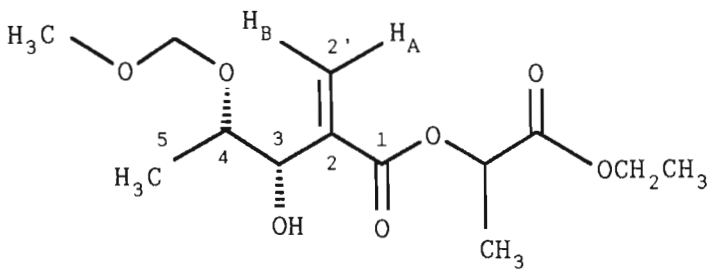
1.11 (3 H, d, *J* 6.5 Hz, H-5)
1.28 (3 H, t, *J* 7.1 Hz, CH_3CH_2)

1.54 (3 H, d, *J* 7.1 Hz, CH_3CHCOO)
2.95 (1 H, d, *J* 4.4 Hz, OH)
3.38 (3 H, s, OCH_3)
4.08 (1 H, dq, *J* 6.4 and 3.9 Hz, H-4)
4.21 (2 H, q, *J* 7.2 Hz, CH_2CH_3)
4.68 (1 H, m, H-**3**)
4.70 (2 H, s, OCH_2O)
5.16 (1 H, q, *J* 7.1 Hz, $CHCOO$)
6.06 (1 H, t, *J* 1.5 Hz, H_B)
6.48 (1 H, overlapping dd, *J* 1.3 and 1.3 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.09 (q, CH_3CH_2)
16.92 (q, C-5 and CH_3CHCOO)
55.52 (q, OCH_3)
61.46 (t, CH_2CH_3)
68.99 (d, $COOCH$)
72.71 (d, C-3)
74.47 (d, C-4)
95.22 (t, OCH_2O)
128.00 (t, C-2')
138.51 (s, C-2)
165.26 (s, C-1)
170.55 (s, $COOCH_2$)

Minor isomer: *syn* **(251 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.22 (3 H, d, *J* 6.4 Hz, H-5)
1.27 (3 H, t, *J* 7.1 Hz, CH_3CH_2)
1.55 (3 H, d, *J* 7.1 Hz, CH_3CHCOO)
3.19 (1 H, d, *J* 6.1 Hz, OH)
3.37 (3 H, s, OCH_3)
3.84 (1 H, dq, *J* 6.4 and 4.8 Hz, H-4)
4.21 (2 H, q, *J* 7.2 Hz, CH_2CH_3)
4.42 (1 H, m, H-3)
4.64 and 4.70 (2 H, AB system, J_{AB} 6.8 Hz, OCH_2O)
5.15 (1 H, q, *J* 7.1 Hz, COOCH)
6.03 (1 H, t, *J* 1.2 Hz, H_B)
6.45 (1 H, dd, *J* 1.1 and 0.6 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.84 (q, CH_3CH_2)
17.48 (q, C-5 and CH_3CHCOO)
55.62 (q, OCH_3)
61.50 (t, CH_2CH_3)
69.04 (d, COOCH)
73.75 (d, C-3)
76.86 (d, C-4)
96.06 (t, OCH_2O)
127.55 (t, C-2')
140.00 (s, C-2)
165.48 (s, C-1)

170.55 (s, $COOCH_2$)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.037

m/z (EI):

245(M^+-45, 8), 229(1), 214(5), 201(100), 186(1), 157(1), 156(6), 155(75), 141(3), 117(1), 101(17), 98(3), 97(13), 89(17), 83(63), 73(11), 70(3) and 54(2).

m/z (CI;CH_4);

291(MH^+, 2), 289(M^+-1, 1), 260(1), 259(100), 229(11), 201(4), 157(2), 141(7), 117(5) and 101(13).

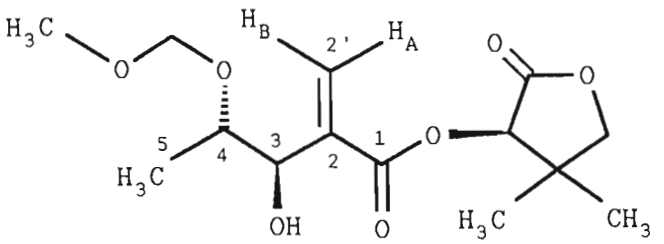
$C_{13}H_{22}O_7$ (290.32) Calculated: C 53.79 H 7.64
Found (mixture): C 53.59 H 7.75

(R)-(-)-Pantolactone ester of [(3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoic acid **(253)**

Application of **GENERAL PROCEDURE 12** aldehyde **(104)** (0.66 g, 5.59 mmol), ester **(78)** (1.029 g, 5.59 mmol) and DABCO **(56)** (0.063 g, 0.59 mmol), using hexane-ethyl acetate (70:30) as eluant, afforded the title compound (0.303 g, **18%**).

$C_{14}H_{22}O_7$ **MW** 302.33

Major isomer: *anti* **(253 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

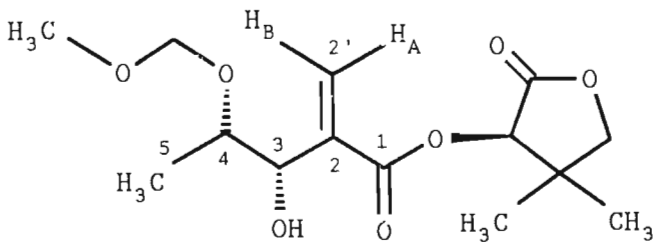
1.13 (3 H, d, *J* 6.5 Hz, H-5)
1.16 (3 H, s, CH_3C)
1.24 (3 H, s, CH_3C)
3.07 (1 H, d, *J* 3.6 Hz, O*H*)
3.38 (3 H, s, OCH_3)
4.00 (1 H, dq, *J* 6.5 and 4.0 Hz, H-4)
4.09 (2 H, s, COOCH_2)
4.70 (2 H, s, OCH_2O)
4.71 (1 H, m, H-3)
5.46 (1 H, s, C*H*COO)
6.15 (1 H, t, *J* 1.4 Hz, H_B)
6.50 (1 H, t, *J* 1.1 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.10 (q, C-5)
20.01 (q, CH_3C)
23.06 (q, CH_3C)
40.56 (s, C$[CH_3]_2$)
55.72 (q, OCH_3)
72.48 (d, C-3)
76.42 (t, $COOCH_2$)
75.55 (d, CHCOO)
75.03 (d, C-4)
95.40 (t, OCH_2O)
128.85 (t, C-2')
138.77 (s, C-2)

165.30 (s, C-1)
172.72 (s, $COOCH_2$)

Minor isomer: *syn* **(253 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.22 (3 H, d, *J* 6.4 Hz, H-5)
1.22 (3 H, s, CH_3C)
1.25 (3 H, s, CH_3C)
3.27 (1 H, d, *J* 6.2 Hz, O*H*)
3.36 (3 H, s, OCH_3)
3.92 (1 H, dq, *J* 6.4 and 4.6 Hz, H-4)
5.47 (1 H, s, COOC*H*)
4.06 (2 H, s, $COOCH_2$)
4.50 (1 H, m, H-3)
4.63 and 4.71 (2 H, AB system, *J* 6.9 Hz, OCH_2O)
6.09 (1 H, t, *J* 1.2 Hz, H_B)
6.50 (1 H, t, *J* 1.1 Hz, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

17.42 (q, C-5)
20.01 (q, CH_3C)
23.06 (q, CH_3C)
40.49 (s, $C[CH_3]_2$)

55.81 (q, OCH_3)
74.14 (d, C-3)
75.68 (d, COOCH)
76.66 (d, C-4)
76.42 (t, $COOCH_2$)
128.69 (t, C-2')
140.01 (s, C-2)
165. (s, C-1)
171.89 (s, $COOCH_2$)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.150

m/z (EI):

213 (M^+-89, 58), 128(18), 113(100), 111(28), 96(20), 89(19), 83(70), 56(53) and 55(53).

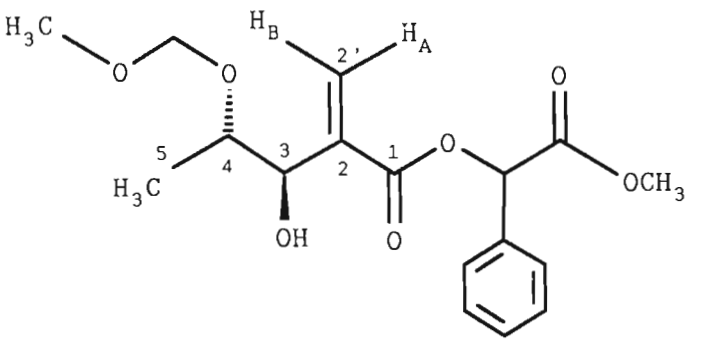
$C_{14}H_{22}O_7$ (302.33) Calculated: C 55.62 H 7.34
Found (mixture): C 55.67 H 7.10

(R)-(-)-Methyl mandelate ester of [(3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoic acid]
(252)

Aplication of **GENERAL PROCEDURE 12** to the aldehyde **(104)** (0.60 g, 5.09 mmol), ester **(80)** (1.12 g, 5.09 mmol) and DABCO **(56)** (0.057 g, 0.59 mmol), using hexane-ethyl acetate as eluant (70:30), afforded the title compound (0.468 g, **27%**).

$C_{17}H_{22}O_7$ **MW** 338.36

Major isomer: *anti* **(252 A)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

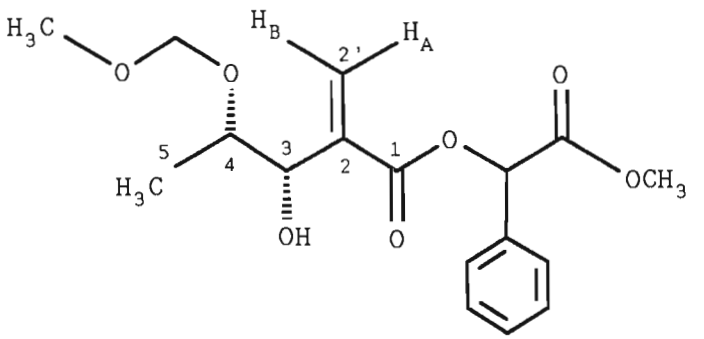
1.12 (3 H, d, *J* 6.5 Hz, H-5)
2.95 (1 H, broad s, O*H*)
3.34 (3 H, s, CH_3OCH_2)
3.74 (3 H, s, $COOCH_3$)
4.02 (1 H, dq, *J* 6.5 and 3.9 Hz, H-4)
4.68 (2 H, s, OCH_2O)
4.74 (1 H, m, H-3)
6.02 (1 H, s, C*H*Ph)
6.14 (1 H, t, *J* 1.5 Hz, H_B)
6.55 (1 H, t, *J* 1.2 Hz, H_A)
7.46 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.86 (q, C-5)
52.69 (q, $COOCH_3$)
55.65 (q, CH_3OCH_2)
72.45 (d, C-3)
74.39 (d, CHPh)
74.65 (d, C-4)
95.22 (t, OCH_2O)
127.60, 128.86, 129.35 (d, CH aromatics)

128.24 (t, C-2')
133.63 (s, *C*CHO aromatic)
138.36 (s, C-2)
165.22 (s, C-1)
169.01 (s, $COOCH_3$)

Minor isomer: *syn* **(252 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

1.24 (3 H, d, *J* 6.5 Hz, H-5)
2.95 (1 H, broad s, O*H*)
3.39 (3 H, s, CH_3OCH_2)
3.74 (3 H, s, $COOCH_3$)
4.16 (1 H, dq, *J* 6.5 and 3.8 Hz, H-4)
4.46 (1 H, m, H-3)
6.03 (1 H, s, C*H*Ph)
6.09 (1 H, t, *J* 1.2 Hz, H_B)
6.56 (1 H, m, H_A)
7.46 (5 H, m, C_6H_5)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.74 (q, C-5)

52.69 (q, $COOCH_3$)
55.69 (q, CH_3OCH_2)
72.99 (d, C-3)
74.39 (d, CHPh)
74.39 (d, C-4)
95.18 (t, OCH_2O)
127.60, 128.86, 129.35 (d, CH aromatics)
128.52 (t, C-2')
133.63 (s, CCHO aromatic)
138.32 (s, C-2)
165.22 (s, C-1)
169.01 (s, $COOCH_3$)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ

Δ (NH_{syn} - NH_{anti}) = 0.167

m/z (CI):

220(M^+-118, 4), 189(4), 188(25), 165(18), 119(1), 118(8), 106(13), 105(100), 90(17), 89(18) and 77(55).

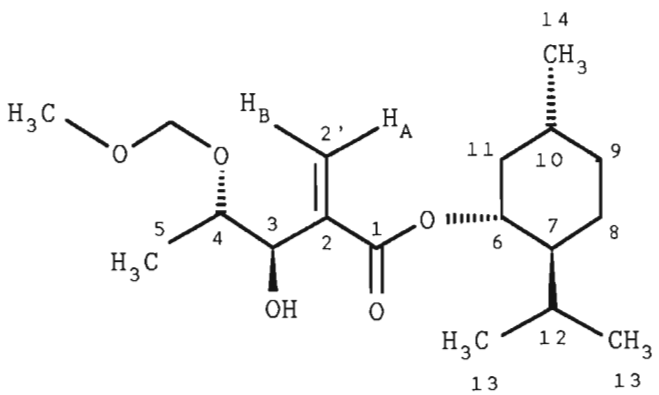
$C_{17}H_{22}O_7$ (338.36) Calculated: C 60.35 H 6.56
Found (mixture): C 60.91 H 6.87

(R)-(-)-Menthol ester of [(3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoic acid **(254a)**

Application of **GENERAL PROCEDURE 12** to the aldehyde **(104)** (1.22 g, 10.34 mmol), (R)-(-)-menthyl acrylate **(151a)** (2.17 g, 10.34 mmol) and DABCO **(56)** (0.464 g, 4.14 mmol), using hexane-ethyl acetate (85:15 and 93:7) as eluant, afforded the title compound (1.39 g, **41%**).

$C_{18}H_{32}O_5$ **MW** 328.45

Major isomer: *anti* **(254 A)**



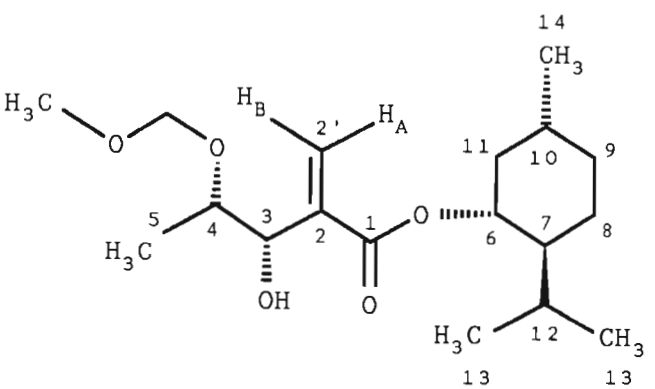
^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.76 (3 H, d, *J* 7.0 Hz, H-14)
0.85 (1 H, m, H-12)
0.90 (3 H, d, *J* 6.1 Hz, H-13)
0.92 (3 H, d, *J* 6.5 Hz, H-13)
1.03 (2 H, m, H-9)
1.10 (3 H, d, *J* 6.4 Hz, H-5)
1.48 (2 H, m, H-8)
1.64 (2 H, m, H-11)
1.81 (1 H, m, H-10)
1.99 (1 H, m, H-7)
3.04 (1 H, d, *J* 4.8 Hz, O*H*)
3.38 (3 H, s, OCH_3)
3.99 (1 H, m, H-4)
4.66-4.85 (2 H, m, H-3 and H-6)
4.69 (2 H, s, OCH_2O)
5.94 (1 H, t, *J* 1.5 Hz, H_B)
6.34 (1 H, overlapping dd, H_A)

^{13}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

13.96 (q, C-5)
16.41 (q, C-14)
20.70 (q, C-13)
22.01 (q, C-13)
23.53 (t, C-9)
26.47 (d, C-12)
31.39 (d, C-10)
34.18 (t, C-8)
40.70 (t, C-11)
47.06 (d, C-7)
55.49 (q, OCH_3)
73.09 (d, C-3)
74.72 (d, C-6)
74.58 (d, C-4)
95.11 (t, OCH_2O)
126.42 (t, C-2')
139.31 (s, C-2)
165.74 (s, C-1)

Minor isomer: *syn* **(254 B)**



^{1}H n.m.r. (200 MHz; $CDCl_3$) δ/ppm:

0.76 (3 H, d, *J* 7.0 Hz, H-14)
0.85 (1 H, m, H-12)

0.90 (3 H, d, *J* 6.1 Hz, H-13)
0.92 (3 H, d, *J* 6.5 Hz, H-13)
1.03 (2 H, m, H-9)
1.11 (3 H, d, *J* 6.5 Hz, H-5)
1.48 (2 H, m, H-8)
1.64 (2 H, m, H-11)
1.81 (1 H, m, H-10)
1.99 (1 H, m, H-7)
3.06 (1 H, d, *J* 4.8 Hz, O*H*)
3.38 (3 H, s, OCH_3)
3.99 (1 H, m, H-4)
4.61 (1 H, m, H-3)
4.69 (2 H, s, OCH_2O)
4.78 (1 H, m, H-6)
5.94 (1 H, t, *J* 1.5 Hz, H_B)
6.34 (1 H, overlapping dd, H_A)

^{1}C n.m.r. (50 MHz; $CDCl_3$) δ/ppm:

14.15 (q, C-5)
16.27 (q, C-14)
20.75 (q, C-13)
22.01 (q, C-13)
23.34 (t, C-9)
26.32 (d, C-12)
31.39 (d, C-10)
34.18 (t, C-8)
40.78 (t, C-11)
47.06 (d, C-7)
55.49 (q, O*C*H_3)
73.17 (d, C-3)
74.72 (d, C-6)
74.85 (d, C-4)
95.16 (t, O*C*H_2O)
126.42 (t, C-2')
139.31 (s, C-2)

165.77 (s, C-1)

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.058

m/z (EI):

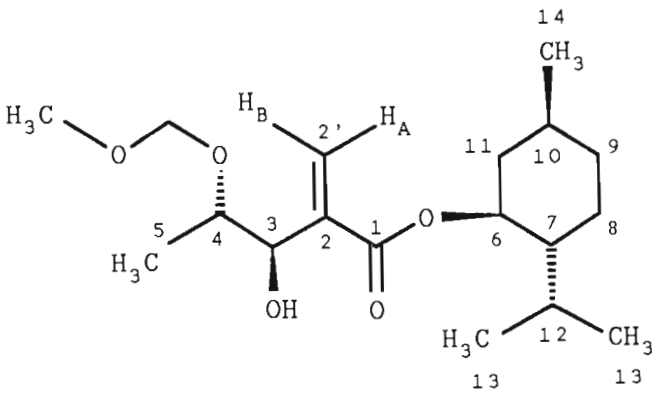
239(M^+-89, 0.4), 221(0.4), 139(18.4), 138(26.8), 123(6.8), 111(8.4), 110(8.4), 101(12.3), 97(20.7), 96(6.9), 89(18.4), 84(13.2), 83(100), 69(28.5), 68(2.6), 55(22.4), 53(2.1), 45(33.2) and 43(5.5).

$C_{18}H_{32}O_5$ (328.45) Calculated: C 65.82 H 9.82
Found (mixture): C 65.74 H 9.73

(S)-(+)-Menthol ester of [(3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoic acid **(254b)**

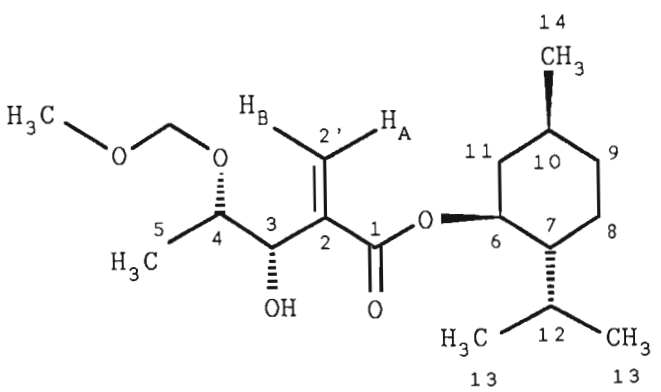
Application of **GENERAL PROCEDURE 12** to the aldehyde **(104)** (0.60 g, 5.09 mmol), (S)-(+)-menthyl acrylate **(151b)** (1.069 g, 5.09 mmol) and DABCO **(56)** (0.571 g, 5.09 mmol), afforded the *crude* product (0.56 g, **34%**).

Major isomer: *anti* **(254 C)**



Not characterised.

Minor isomer: *syn* **(254 D)**



Not characterised.

^{1}H n.m.r. (200 MHz; $CDCl_3$ + *TAI*) δ/ppm:

Δ (NH_{syn} - NH_{anti}) = 0.056

5.2.17 TRANSESTERIFICATION OF THE (CHIRAL ALDEHYDE-CHIRAL ESTER) PRODUCTS.

GENERAL PROCEDURE 13:

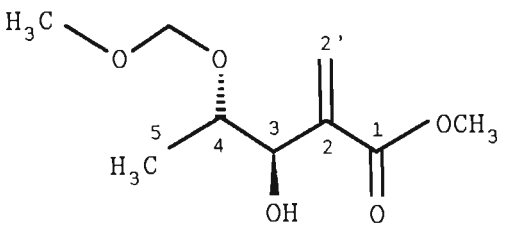
Transesterification of the acrylates with methanol.

A mixture of the crude acrylate (1 equivalent), catalyst (1 equivalent) and methanol (excess) was refluxed until t.l.c. monitoring indicated consumption of the starting material, (See TABLE 34). The cooled reaction mixture was concentrated under reduced pressure, and sequentially washed with saturated sodium hydrogen carbonate solution, dilute (2 N) hydrochloric acid and water. The organic layer was dried and concentrated under reduced pressure to afford the crude (*anti*-enriched) product. Ratio analysis was carried out directly on the crude diastereomeric mixture, by ^{1}H n.m.r.

Methyl (3R, 4S) and (3S, 4S)-3-hydroxy-2-methylene-4-(methoxymethoxy)pentanoate **(131)**

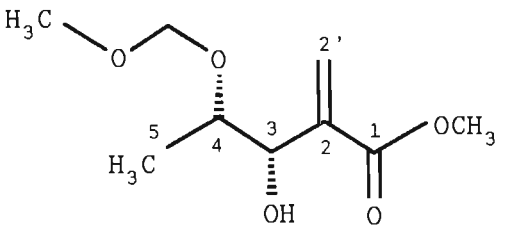
Application of **GENERAL PROCEDURE 13** to the mixture **(251)** (0.20 g, 0.69 mmol), using DABCO **(56)** (0.077 g, 0.69 mmol), afforded the crude product.

Major isomer: *anti* **(131 A)**



See *Section 5.2.7.2* for spectral data, etc.

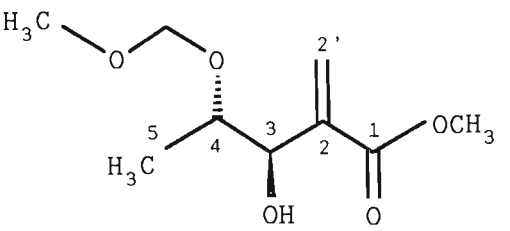
Minor isomer: *syn* **(131 B)**



See *Section 5.2.7.2* for spectral data, etc.

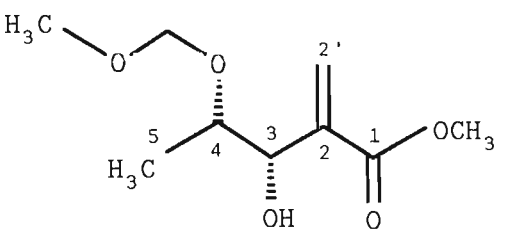
Application of **GENERAL PROCEDURE 13** to the mixture **(252)** (0.59 g, 1.74 mmol), using DMAP (0.203 g, 1.74 mmol), afforded the crude product.

Major isomer: *anti* **(131 A)**



See *Section 5.2.7.2* for spectral data, etc.

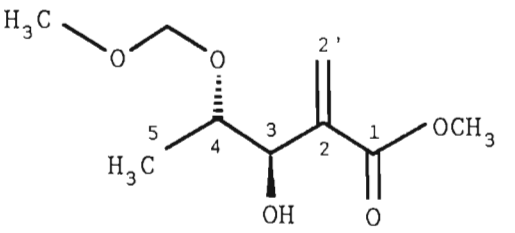
Minor isomer: *syn* **(131 B)**



See *Section 5.2.7.2* for spectral data, etc.

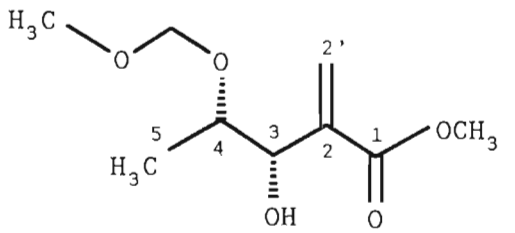
Application of **GENERAL PROCEDURE 13** to the mixture **(253)** (1.78 g, 5.89 mmol), using DMAP (0.72 g, 5.89 mmol), afforded the crude product.

Major isomer: *anti* **(131 A)**



See *Section 5.2.7.2* for spectral data, etc.

Minor isomer: *syn* **(131 B)**



See *Section 5.2.7.2* for spectral data, etc.

CHAPTER 6

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CHAPTER 7.

7. MISCELLANEOUS.

7.1 PUBLICATIONS THAT HAVE RESULTED FROM THIS INVESTIGATION.

1. S. E. Drewes, T. Manickum and G. H. P. Roos, Stereoselective synthesis of α-methylene-β-hydroxy-γ-alkoxy esters and ketones, *Synth. Commun.*, 1988, **18**, 1065.
2. G. H. P. Roos, T. Manickum and D. G. Malissar, A facile diagnostic ^{1}H n.m.r. method for *syn* and *anti* hydroxy systems, *J. Chin. Chem. Soc.*, 1992, **39**, 105.
3. T. Manickum and G. Roos, Stereoselective addition of methyl acrylate to α-amino aldehydes, *Synth. Commun.*, 1991, **21**, 2269.
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5. J. S. Field, T. Manickum, N. Ramesar and G. H. P. Roos, Isolation and structure of a novel secondary Baylis-Hillman coupling product, *S. Afr. J. Chem.*, 1992, submitted (November 1992) for publication.
6. J. S. Field, T. Manickum, N. Ramesar and G. H. P. Roos, X-Ray confirmation of the stereosubstructure determination of some diastereoselective Baylis-Hillman reaction products, *J. Chin. Chem. Soc.*, 1992, submitted (December 1992) for publication.

7.2 ADDENDUM.

Since the conclusion of this study, the following reports, concerning the general Baylis-Hillman reaction and its reversibility, have appeared:

1. H. M. R. Hoffmann, A. Gassner and U. Eggert, *Chem. Ber.* 1991, **124**, 2475.
2. Y. Fort, M-C. Berthe and P. Caubère, *Synth. Commun.*, 1992, **22**, 1265.
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