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Studies on Stereocontrolled Syntheses of α-Hydroxy, α-*N*-Hydroxyamino, α-Oxyamino, and α-Hydrazino Acids for Inhibition of Enzymes

BY

Makarand P. Gore

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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Supervisor

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External Examiner

Date September 21, 1987.

To my mother,

Abstract

Preparation of homochiral α-hydroxy acid derivatives by enolate oxidation and conversion of these to amino acid analogs (α-*N*-hydroxyamino, α-oxyamino, and α-hydrazino acids) were investigated.

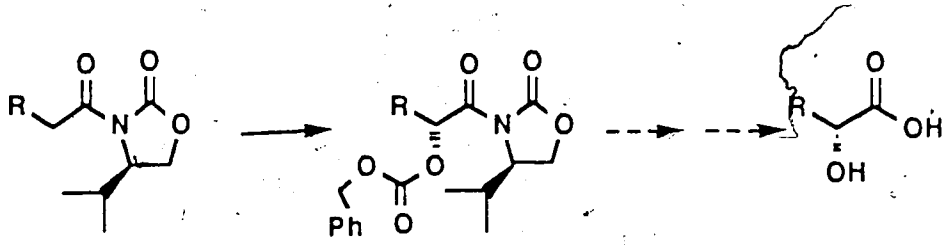
Enolates of chiral carboximides (R = phenyl, ethyl, isopropyl, benzyl) generated using lithium bis(trimethylsilyl)amide react with dibenzyl peroxydicarbonate at -78 °C in tetrahydrofuran to produce benzyl carbonates of the corresponding 2'-hydroxy derivatives in 46 - 89 % yield with ≥ 94:6 diastereoselectivity. With simpler achiral enolates of ketones and esters, the yields of this reaction are usually lower (45 - 71 %) and depend on the method of enolate formation. Potassium enolates (formed with K N(Si Me_3)$_2$) or amine-free lithium enolates (formed from silyl enol ethers and butyllithium) generally give the best yields.

(4*R*, 2' *R*)-3-(2-Hydroxy-1-oxobutyl)-4-isopropyloxazolidin-2-one, prepared in quantitative yield from the corresponding benzyl carbonate derivative, and *R* and *S* enantiomers of dibenzyl and dimethyl esters of malic acid were converted to the corresponding trifluoromethanesulfonate (triflate) derivatives. Reaction of the triflates with *O*-benzylhydroxylamine produced 54 - 89 % yields of protected α-*N*-hydroxyamino acids.

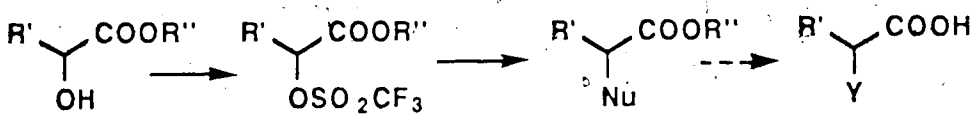
Reaction of the triflates derived from *R* and *S* benzyl malate with lithium *tert*-butyl-*N*-hydroxycarbamate produced protected α-oxyamino acids in 42 - 62 % yields, with 88 - 96 % stereoselectivity. These compounds were deprotected to give α-oxyaminosuccinic acids in > 80 % yield. Similar reaction of the triflates with benzyl carbazate furnished

protected α-hydrazino acids in ≥ 89 % yields and with ≥ 99 % stereoselectivity. The *R* and *S* α-hydrazinosuccinic acids were obtained from these in 52 - 74 % yield.

The compounds were tested by Dr. Monica Palcic (Food Science Dept., University of Alberta) for inhibition of aspartate α-decarboxylase and aspartate aminotransferase . The L- α-oxyaminosuccinic acid is an extremely potent competitive inhibitor of aspartate aminotransferase.



R = phenyl, ethyl, isopropyl, benzyl



Y = $NHOH$, ONH_2, $NHNH_2$

Acknowledgements

I am most grateful to my supervisor, Dr. John C. Vederas, for his help and support during my studies. Dr. Monica Palcic and co-workers are thanked for their collaborative effort in testing the amino acid analogs for inhibition of enzymes. I thank the members of our research group for helpful discussions: especially Dr. Leslie D. Arnold, Dr. Laird A. Trimble, and Dr. Bernard J. Rawlings for their help at various points in the synthetic work. Thanks are due to Professor David Evans (Harvard University) for a preprint of his report on oxidation of carboximide enolates. Financial assistance from the Alma Mater Fund of the University of Alberta and Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Ac	CH_3CO
ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
CBZ	benzyloxycarbonyl
CI	chemical ionization
DCC	1,3-dicyclohexylcarbodiimide
DBAD	dibenzylazodicarboxylate
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
ee	enantiomeric excess
Enz	enzyme
Et	ethyl
EtO	Acethyl acetate
FAB	fast atom bombardment
FSOT	fused silica open tubular
GC	gas chromatography
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
IR	infrared spectroscopy
K HMDS	potassium bis(trimethylsilyl)amide

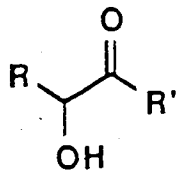
LDA	lithium diisopropylamide
Li HMDS	lithium bis (trimethylsilyl)amide
Mc	menthyl
MCPBA	metachloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
MoOPH	MoO_5 • HMPA • Py
MS	mass spectrometry
MTPA	2-methoxy-2-trifluoromethyl-2-phenylacetyl
NMR	nuclear magnetic resonance
PAL	phenylalanine ammonia lyase
Ph	phenyl
PLP	pyridoxal phosphate
Py	pyridine
RNA	ribonucleic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylchlorosilane
Triflate	trifluoromethanesulfonate ester

Chapter 1

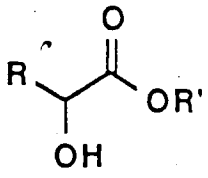
Studies on Enolate Oxidations

I. INTRODUCTION

α-Hydroxy carbonyl compounds **1** are structural subunits of a large number of natural products[1, 2] and are important synthetic intermediates. The homochiral α-hydroxy acids and esters **2** and their derivatives are extensively used in asymmetric synthesis [3, 4] as chiral synthons, derivatising agents, and as chiral ligands.



1



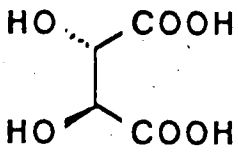
2

For example, the α-hydroxy carbonyl moiety **1** occurs in cortisone and related steroid hormones, [5] in antibiotics such as tetracycline, [6] and in antineoplastic drugs such as vinblastine,[7] adriamycin and daunomycin.[8]

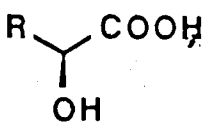
α-Hydroxy carbonyl compounds are intermediates in the preparation of α-fluoro aldehydes,[9] α,β-unsaturated ketones,[10] acyloxiranes,[11] furanones,[12] furans,[13] unsaturated lactones,[14, 15] cyclopentane-2-enones,[16] imidazoles,[17] 2, 2'- azoimidazoles,[18] and spirovetivanes.[19, 20] Silylated derivatives of **1** have been used in stereocontrolled aldol reactions.[3]

The D and L forms of tartaric acid are used as chiral ligands in the

Sharpless epoxidation[21] and are employed as chiral starting materials in the preparation of the sex pheromone of the female gypsy moth, [22] and in the synthesis of desacetyl anisomycin.[23] L-Malic acid is used for the preparation of an intermediate in prostaglandin synthesis.[24] L- Ethyl lactate is a chiral building block in the synthesis of nonactic acids, which are subunits of the antibiotic nonactin.[25, 26] Mandelic acid is used for preparation of chiral derivatives for NMR studies,[27,28] and can be employed for resolution of alcohols.[29]



L- Tartaric acid



R = Ph, L-Mandelic acid

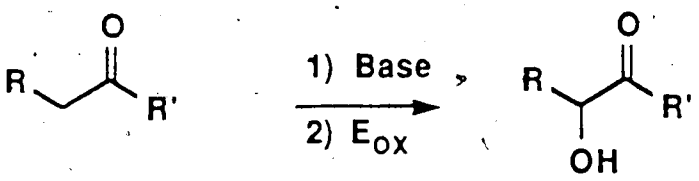
R= CH_3, L- Lactic acid

R= CH_2COOH, L-Malic acid

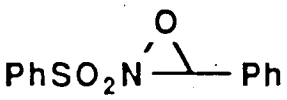
The importance of 1 and 2, as illustrated by the few examples above, has encouraged a variety of methods for their preparation. Apart from the acyloin condensation and modifications,[30 -34] direct oxidation of enolates of carbonyl compounds (figure 1) and oxidation of intermediate derivatives of an enol (figure 2) are the most commonly used methods for preparation of 1. Oxidation of enolates can be performed using phenyl sulfonyl oxaziridine derivatives,[35, 36] molybdenum peroxide : HMPA-pyridine complex (MoOPH),[37, 38] molecular oxygen with *in situ* reduction of peroxides formed in the reaction,[39, 40] and iodoso benzene derivatives. [41 - 44] Although Schank [45 - 48] and Lawesson[49 - 51] have

reported oxidations using acyl peroxides and peroxydicarbonates, the studies are limited to oxidation of enolates of β dicarbonyl compounds, Grignard reagents, or enolates of enamines derived from β dicarbonyl compounds. A recent publication, which is a part of this study, describes the use of dibenzyl peroxydicarbonate as a reagent for oxidation of enolates of monocarbonyl compounds.[52]

Figure 1. Preparation of α-hydroxy carbonyl compounds by enolate oxidation.

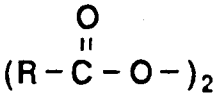


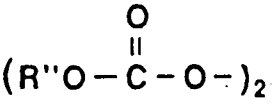
E_{ox} =

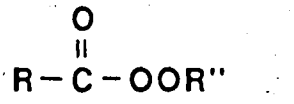


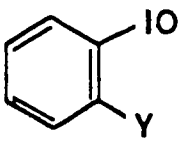
MoO_5.HMPA.Py

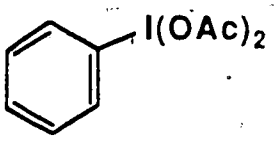
O_2







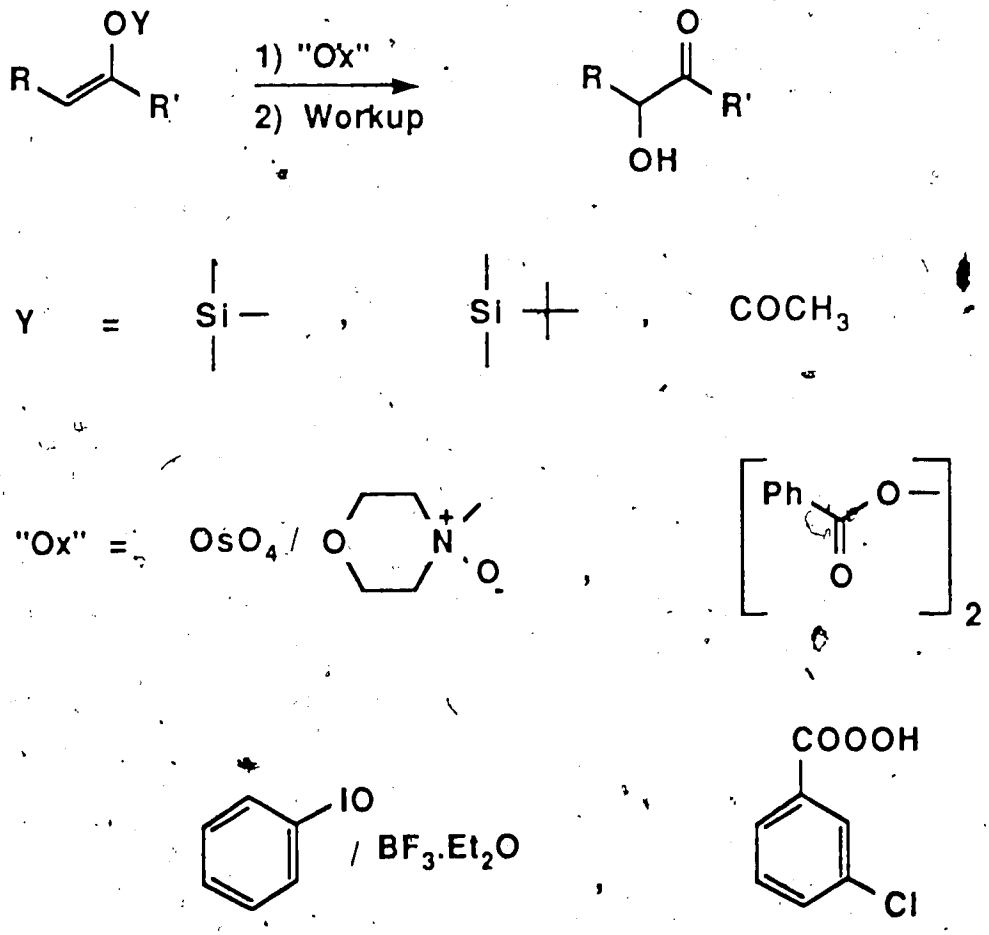




Y = H, COOH

Transformation of silyl enol ethers to 1 is achieved using osmium tetroxide / N-methylmorpholine N-oxide,[53] benzoyl peroxide and irradiation,[54] triphenylphosphite ozonide (in the case of α,β-enones),[55] iodosobenzene and boron trifluoride-etherate,[56] MCPBA,[57 - 60] p-nitrophenylsulfonyl peroxide,[61] phenylsulfonyl oxaziridines,[62] lead tetracarboxylates,[63] and chromyl chloride.[64] Acyloxylation has been reviewed.[65, 66]

Figure 2. Preparation of α-hydroxy carbonyl compounds via derivatives of enols



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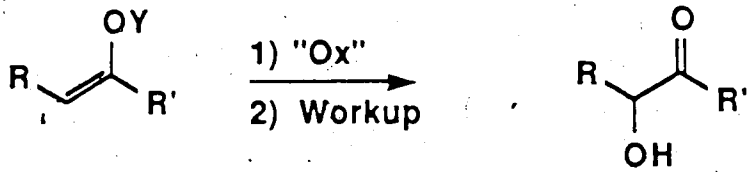
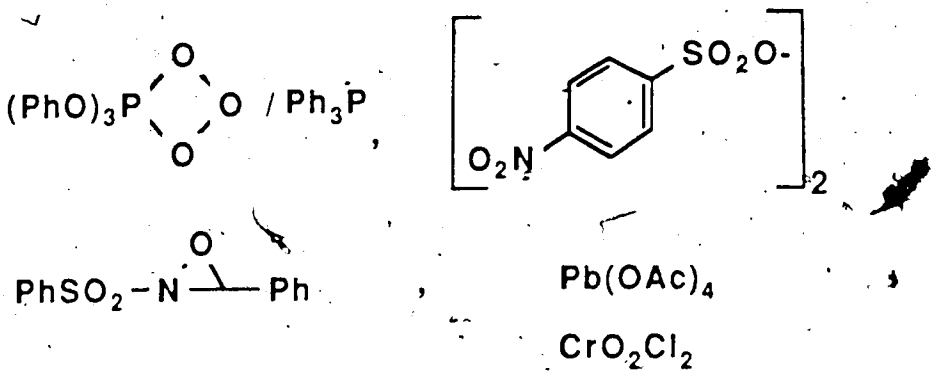
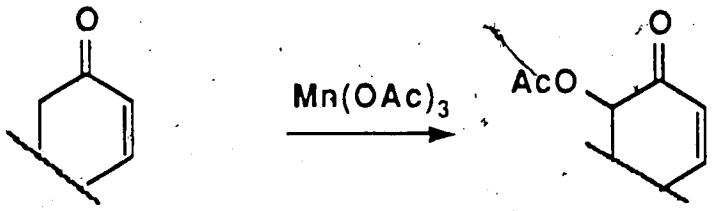
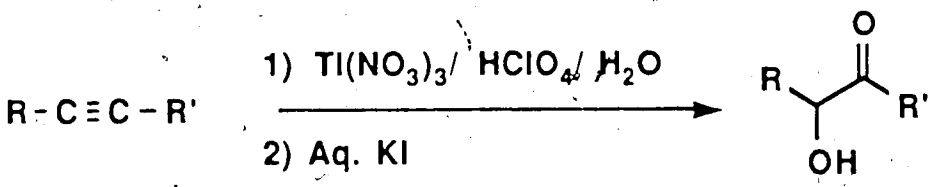




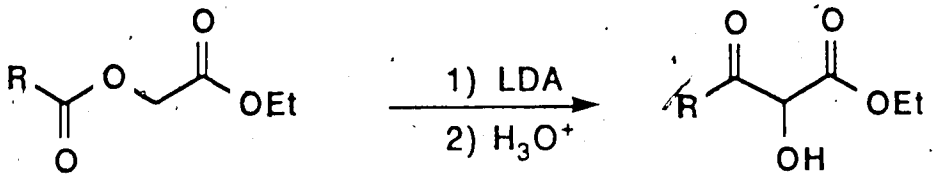
Other oxidative methods for preparation of α-hydroxy carbonyl compounds include oxidation of enones to the corresponding α'-acetates by manganese triacetate, [67] and thallium (III) nitrate oxidation of acetylenes.[68]





Several methods not involving oxidation of enols or enolates are shown in figure 3, but the scope of many of these reactions appears to be limited. α-Hydroxy β-ketoesters can be prepared by rearrangement of α-acyloxy acetates.[69] Condensation of methyl thiomethyl p-toluenesulfones with aldehydes followed by hydrolysis also produces 1:[70] Many procedures involving addition of alkyl lithium reagents, Grignard reagents, and carbanions to aldehydes, ketones, α-silyloxy nitriles, and esters followed by suitable hydrolytic and / or deprotection steps are also employed.[71-82]

Figure 3. Preparation of α-hydroxy carbonyl compounds by methods other than oxidation



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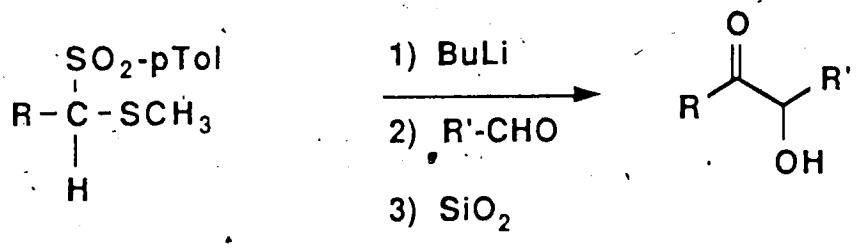

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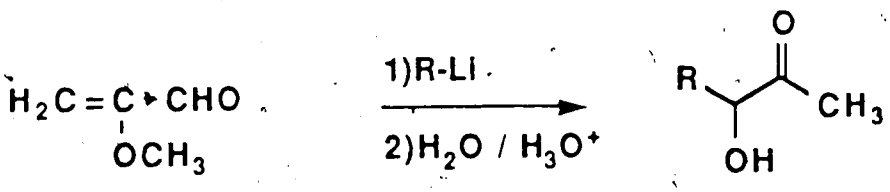

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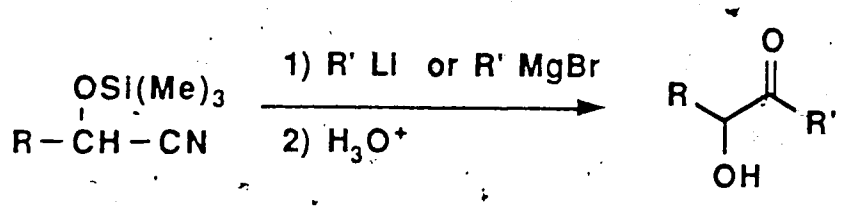
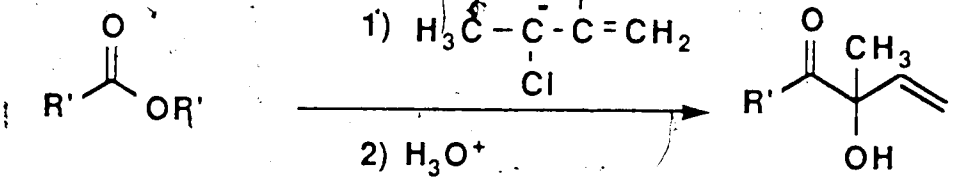


Ref 72, 73



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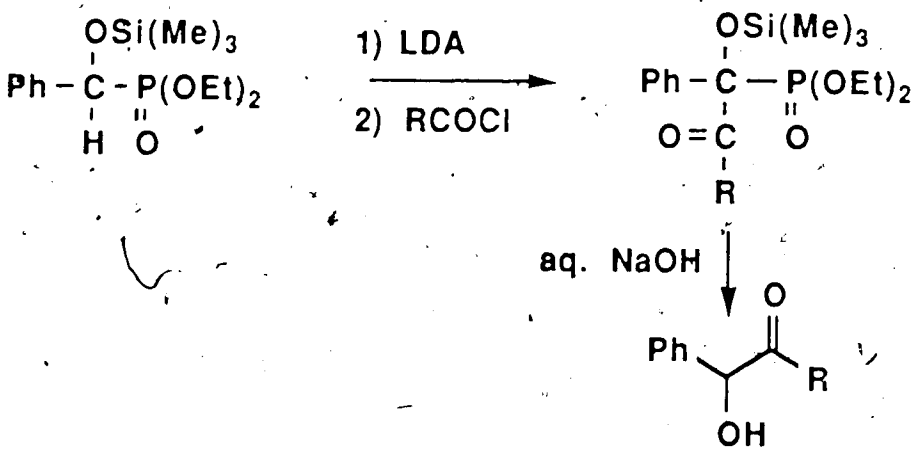

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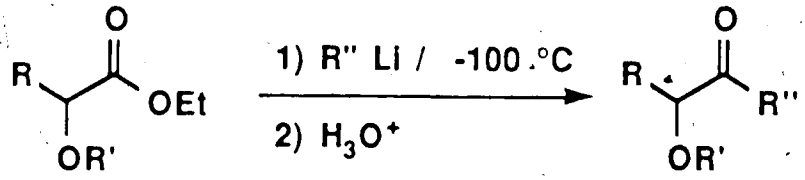

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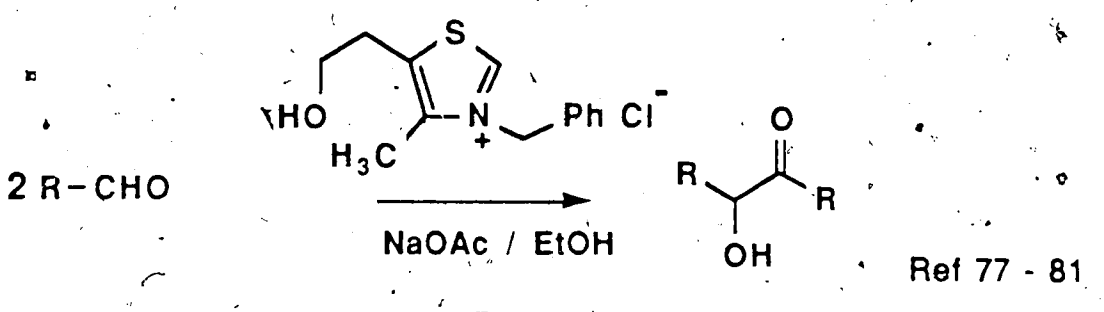
Figure 3. continued...



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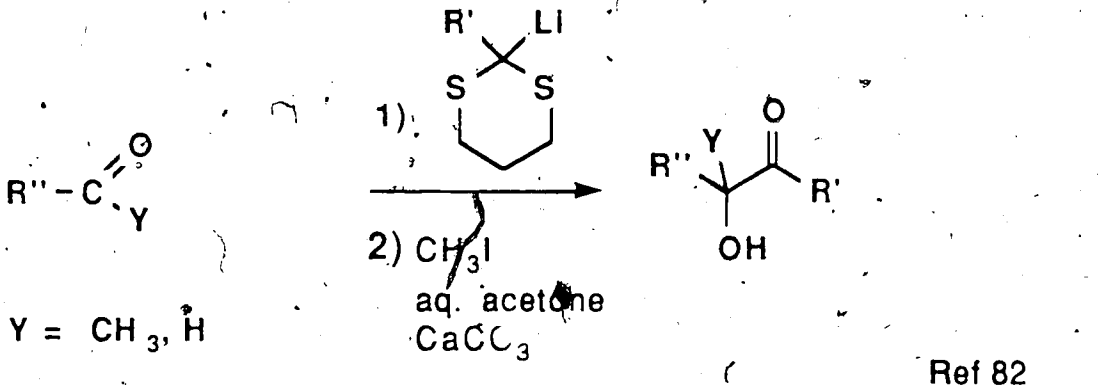
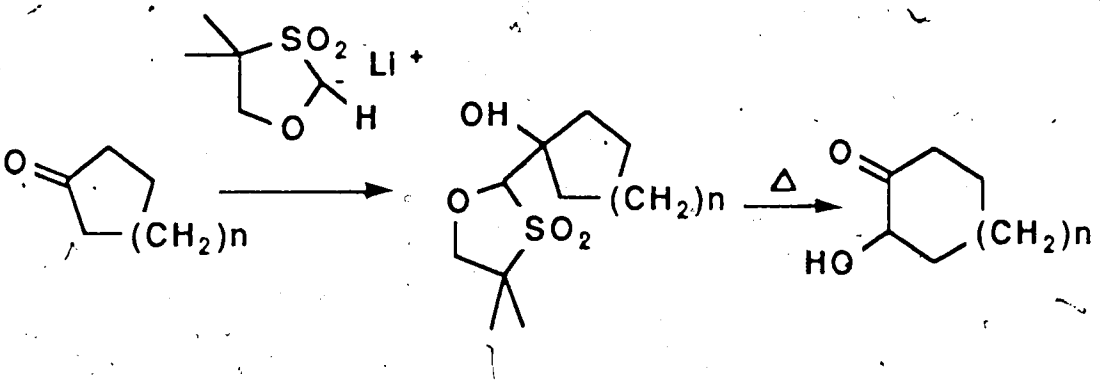
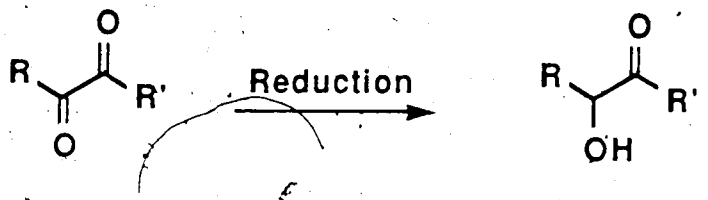


Ref 82

Gokel and Gerdes have found an interesting method for ring expansion of cyclic ketones via hydroxy oxathiolanes to produce cyclic acyloins.[83, 84]



Reduction of α-keto esters using titanium trichloride [85] and 1,2 diketones using zinc [86] to furnish α-hydroxy esters and ketones is also possible.

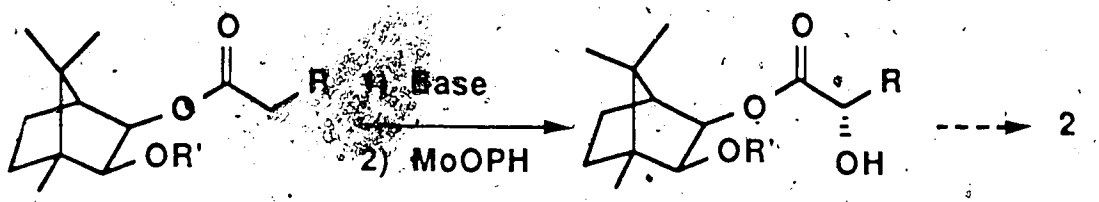


R' = Alkyl, aryl; Reagent Zn / DMF

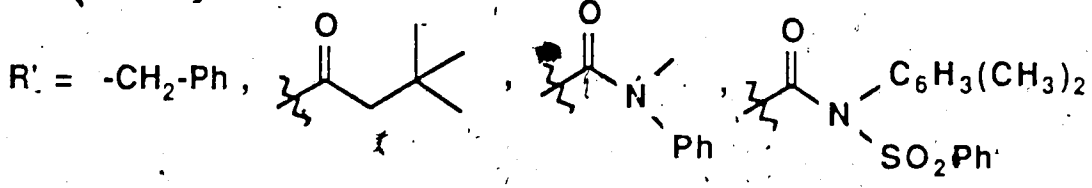
R' = Alkoxy; Reagent $TiCl_3$

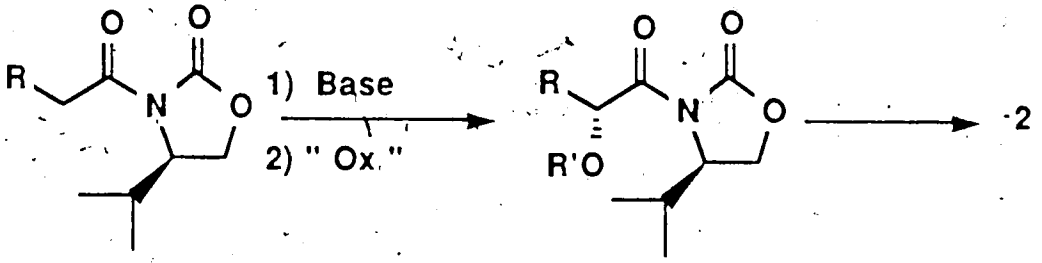
A convenient method for the preparation of 2 by stereocontrolled enolate oxidation was not available at the onset of this work. However, reports by Tamm,[87 - 89] Evans,[90] Davis, [91] and Oppolzer [92] have appeared while the work was well advanced in our laboratories. The methods (figure 4) involve oxidation of an enolate or silyl derivative of an enol generated from an amide or ester bearing a chiral auxiliary. The desired acid or its derivative can be generated by nondestructive removal of the chiral auxiliary. This approach was successfully applied by Evans and co-workers to oxidations,[90] using phenylsulfonyl oxaziridine [62] as the oxidising reagent, in their elegant studies associated with the use of oxazolidinone carboximides for stereocontrolled reactions. Tamm and co-workers have used camphor derivatives as a chiral auxiliaries in their study, while Davis has reported use of 2-alkoxymethylpyrrolidine.

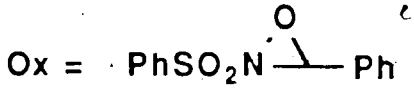
Figure 4. Preparation of α-hydroxy acid derivatives by stereocontrolled oxidation.



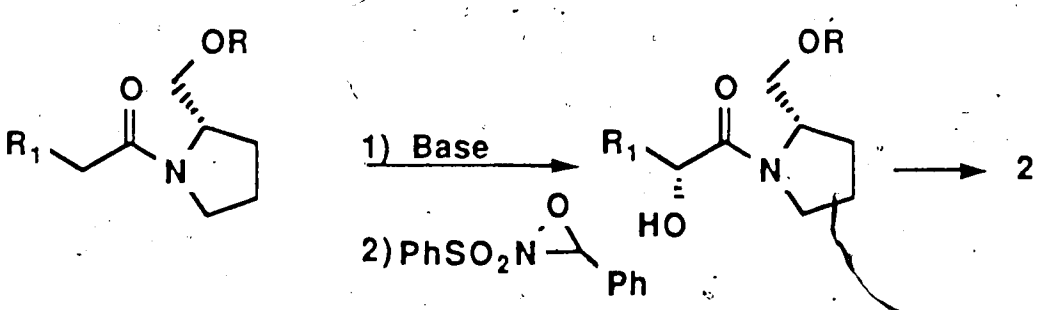
Yields 25 - 90 %, de 14 - 98 %





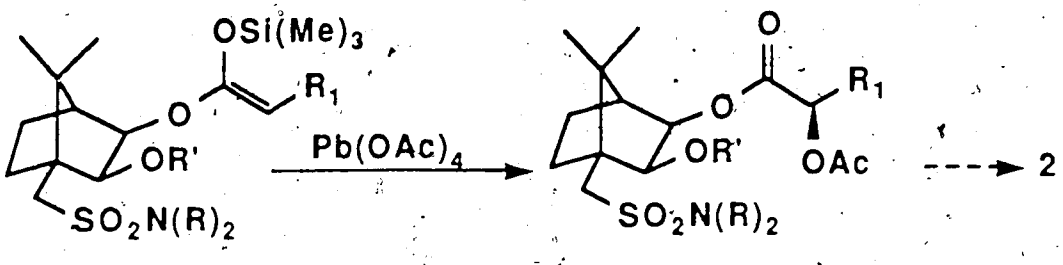


Yields > 85 %, ee 80 - 99 %

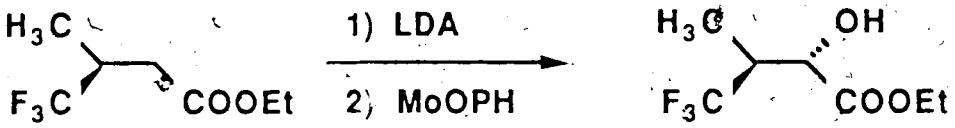


Yields 60 - 96 %, ee 17 - 95 %

Oppolzer and co-workers have developed *iso* -borneol sulfonamide derivatives as chiral auxiliaries for conversion of silylated ketene acetals to α-hydroxy acids. α-Hydroxy β-trifluoromethyl esters have been prepared from β trifluoromethyl esters using MoOPH with good diastereoselectivity.[93]

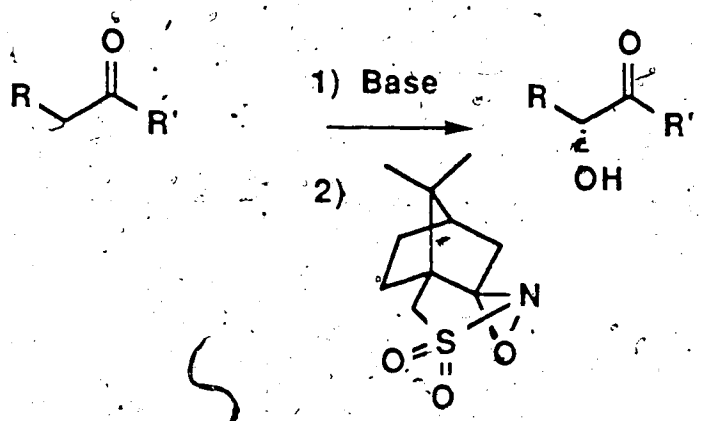


Yields 55 - 67 %, de 88 - 96 %

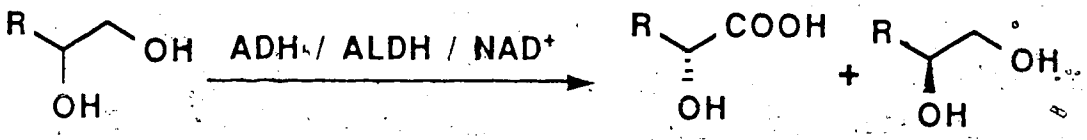


Yield 75 %, de 94 %

Davis and co-workers have recently reported the use of a chiral reagent for stereocontrolled oxidation of achiral enolates with moderate stereoselectivity.[94, 95] An enzymatic system for oxidation of diols that utilises alcohol dehydrogenase and aldehyde dehydrogenase, gives homochiral α-hydroxy acids.[96]



Yields 35 -88 %, ee 18 - 85 %



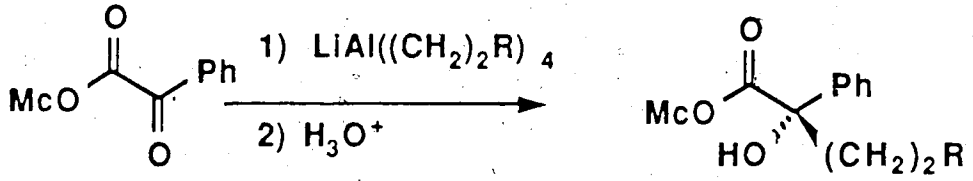
Yields < 50 %, ee 97 %

ADH = Alcohol dehydrogenase

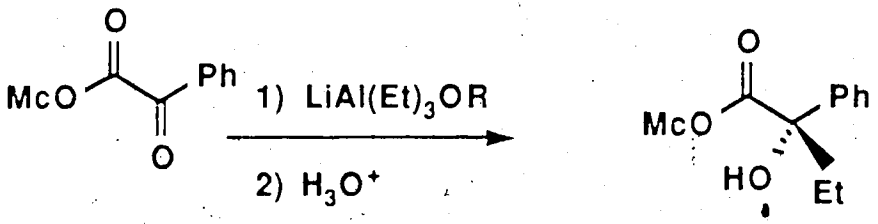
ALDH = Aldehyde dehydrogenase

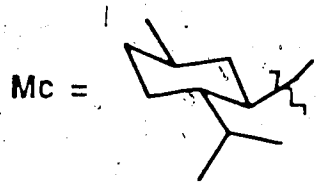
Reductive alkylation and reduction of α-keto menthyl esters studied by Boireau and co-workers [97, 98] and reduction of 1-carboxymethyl pyrrolidine α-keto amides described by Soai and co-workers [99] are examples of the use of chiral auxiliaries for stereocontrolled reductions to prepare **2** (figure 5). Reduction[100] of achiral α-keto esters to **2** employing a chiral α-pinene borane reagent proceeds with excellent stereoselectivity.

Figure 5. Preparation of α-hydroxy acid derivatives by stereocontrolled reduction and reductive alkylation

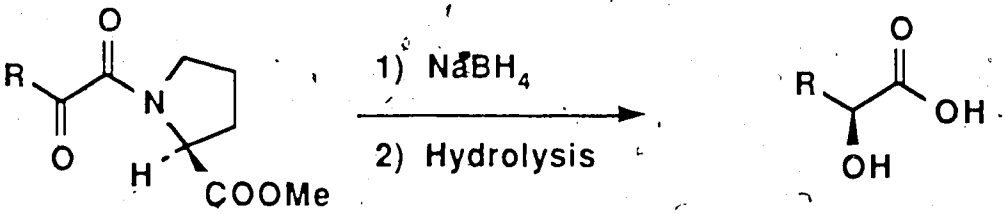


Yields 58 - 80 %, de 64 - 76 %

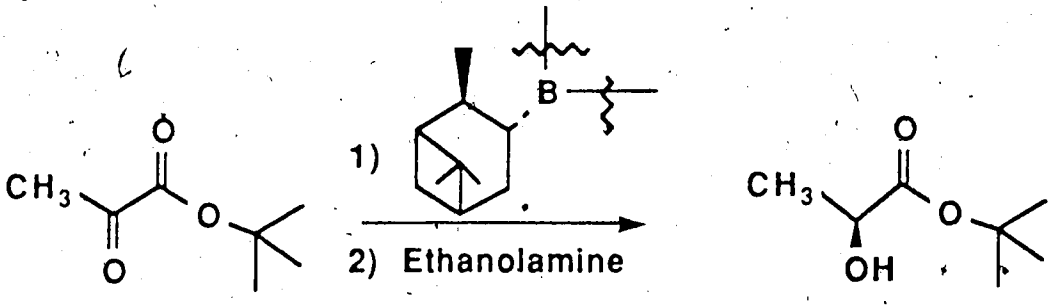




Yields 73 - 77 %, de 69 - 84 %

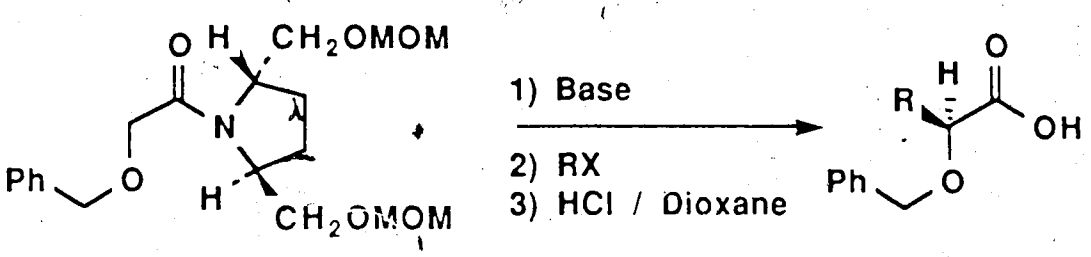


Yields not reported, ee 0 - 64 %



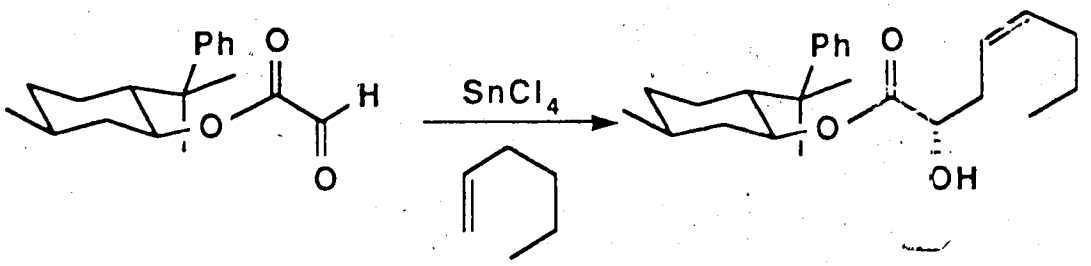
Yields 50 - 89 %, ee 72 - 99 %

Investigations by Katsuki show that alkylation of chiral α-benzylalkoxy amides followed by hydrolysis affords **2**.[101] Wipf tesell has found an interesting ene reaction involving glyoxylate esters of menthol and its analogs.[102]



MOM = Methoxymethyl

Yields 65 - 92 %, ee > 96 %



Yields 20 - 95 %, de > 95 %

Many of the methods described above suffer from certain disadvantages such as limited scope of application, low yields or low chiral purities, difficult access to starting materials, or multiple steps. In contrast, direct oxidation of either chiral or achiral enolates is a very versatile approach. Our interest in oxygen-18 labeling studies,[103] and in preparation of **2** which we planned to use in syntheses of enantiomerically pure amino acid analogs (Chapter 2) for inhibition of enzymes, led to a search for a reagent that would accomplish stereoselective oxidations of enolates and that could also be readily prepared from ^{18}O labeled oxygen

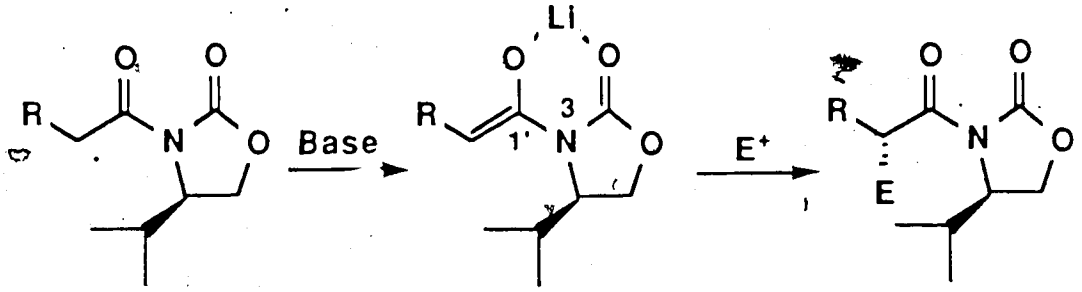
gas or hydrogen peroxide.[104] Preparation of the labeled oxaziridine reagent would require several steps while the more accessible MoOPH often gives low yields.[90] Direct oxygenation using O_2 gas is less likely to allow stereochemical control[105] and is problematic if the product still bears hydrogen at the α-carbon.[40] A convenient method suitable for such stereospecific oxidation was not available at the outset of our study, and the development of a suitable reagent to prepare **2** seemed to be highly desirable.

II. Results and Discussion

Development of a method of enolate oxidation for the preparation of **2** with high enantiomeric purity requires consideration of several factors. Ideally it should produce high yields of the products. Preparations of **2** involving use of a chiral auxiliary would require that the auxiliary be readily accessible and easily attached to a substrate. The chiral enolate produced from such a compound should allow high diastereoselectivity during the oxidation process, and the auxiliary should be easily cleaved to give the required α-hydroxy acid or its derivative.

Elegant studies by Evans and co-workers have shown that the chiral enolates derived from oxazolidinone carboximides shown in scheme 1, afford a high degree of diastereoselectivity and excellent yields of products upon reaction with a variety of electrophiles (scheme 1).[90,106-109]

Scheme 1



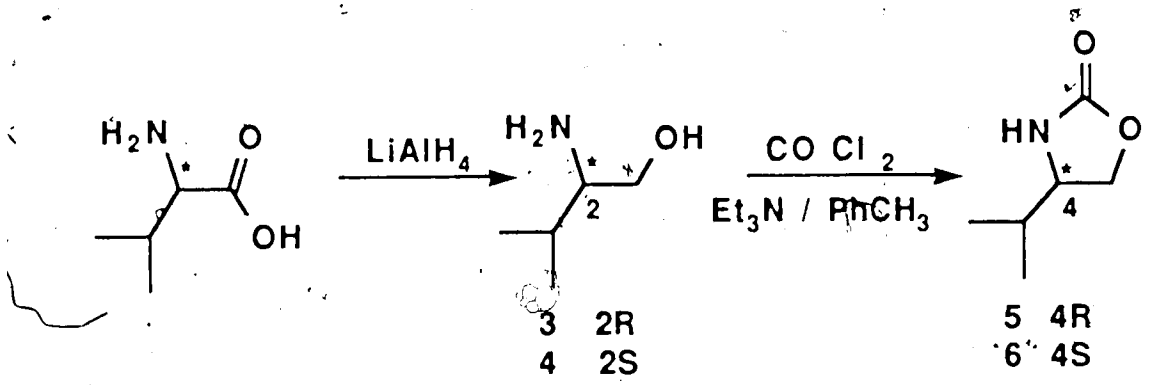
There are three factors, proposed by Evans, that appear to be responsible for the high degree of diastereoselection observed in the reaction. The bulk of the isopropyl moiety leads to predominant formation of the Z enolate. Strong complexation of the lithium counterion to the oxazolidinone carbonyl

and enolate oxygens restrains the rotation around the bond between nitrogen 3 and carbon 1' of the enolate. Finally, the bulky isopropyl group directs the electrophile from the *re* face.

Hence, the oxidation of the chiral imide enolate using an electrophilic oxidising reagent seemed to be a promising approach for preparation of **2**. A report by Evans [90] appeared in print describing similar studies using a phenylsulfonyl oxaziridine reagent [36] while our work was well advanced.

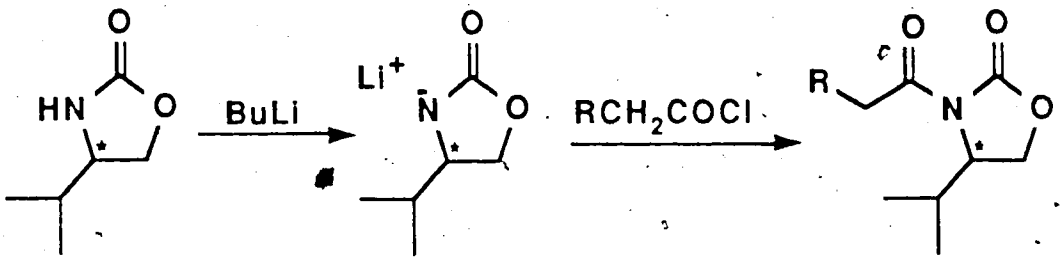
The first objective was to prepare the chiral auxiliary. D or L-Valine can be reduced with $LiAlH_4$ in high (> 80 %) yields to valinols **3** and **4** , which can be easily transformed to oxazolidinones **5** and **6** [110, 111] (scheme 2).[112] Reaction of L-valinol **3** with phosgene under basic conditions afforded oxazolidinone **5** in 77 % yield. Similar treatment of **4** gave oxazolidinone **6**.

Scheme 2.

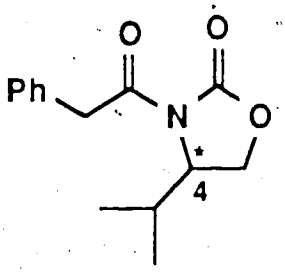


The desired oxazolidinone carboximides could be easily prepared by reaction of the anion generated from **5** or **6** using butyllithium with the appropriate acid chloride (scheme 3).[90, 106 - 111]

Scheme 3.

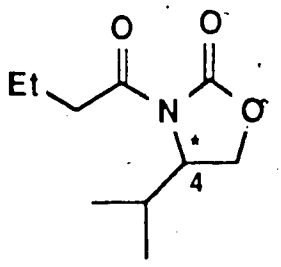


Preliminary studies employed the phenylacetyl and butanoyl derivatives 7, 8, 9 and 10.



7 4R

8 4S



9 4R

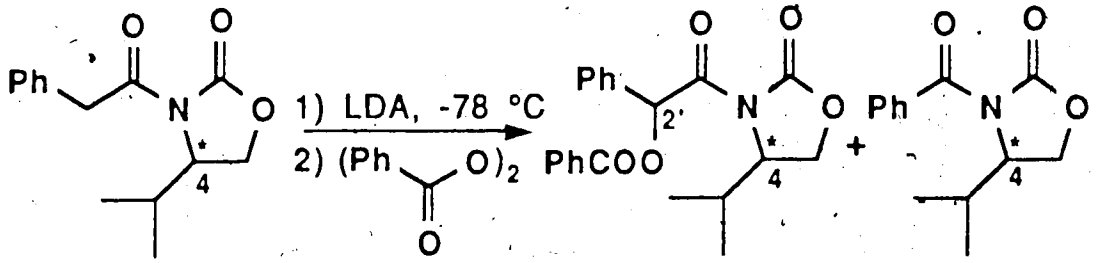
10 4S

Initial attempts to oxidise carboximide enolates utilised the MoOPH reagent, which is accessible in two steps from hydrogen peroxide and molybdenum (VI) oxide.[38] Treatment of molybdenum (VI) oxide with hydrogen peroxide produced MoO_5, which was not isolated, but treated directly with HMPA. The yellow crystalline solid obtained was dried in high vacuum over P_2O_5 and was treated with pyridine to give the MoOPH reagent. The enolates of the carboximides 7 - 10 were generated at - 78

°C using LDA (lithium diisopropylamide) and treated with MoOPH. These reactions produced very complex mixtures from which ~15 % of deacylated oxazolidinone **5** or **6** could be isolated. Although ^{1}H NMR spectra of the mixture obtained from oxidation of **9** or **10** showed the oxidation product was formed in ~ 20 % yield, material of satisfactory purity could not be obtained, and the efforts using MoOPH were abandoned.

Shank [48] and Lawesson[49] have shown that Grignard reagents and enolates of imines of β dicarbonyl compounds attack benzoyl peroxide at the peroxy oxygen. Based on this precedent, oxidations using benzoyl peroxide seemed promising (scheme 4). Oxidations of enolates generated as above from **7** and **8** gave the expected oxidised products **11** and **12**, respectively, in low (~21 %) yield along with side products **13** and **14** in ~14 % yield.

Scheme 4.



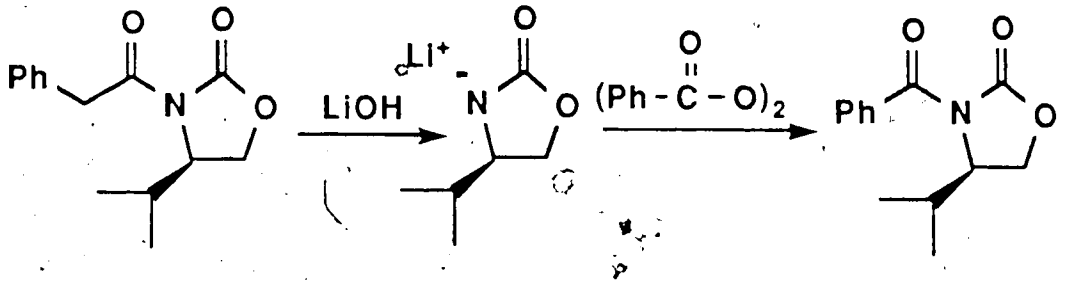
7, 4R **11, (4R, 2'R)** **13, 4R**

8, 4S **12, (4S, 2'S)** **14, 4S**

Since commercially available benzoyl peroxide contains water, hydroxide may be generated in the reaction. Products **13** and **14** may arise from the cleavage of the side chain of the carboximide by hydroxide followed by

attack of the anion of **5** and **6**, respectively, on the carbonyl carbon of benzoyl peroxide (scheme 5). The butanoyl compound showed similar behavior. The oxidation of butanoyl derivative **10** gave a complex mixture from which only 32 % of the desired product **16** could be isolated.

Scheme 5.

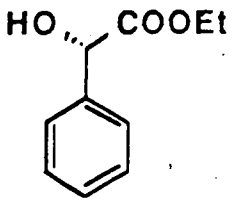


7 **13**

In order to avoid this possible complication, benzoyl peroxide was carefully dried over anhydrous $MgSO_4$ and 4 Å molecular sieves as a THF solution. Davis and co-workers have reported that use of lithium bis(trimethylsilyl)amide (LiHMDS) instead of LDA produces better yields of products in enolate oxidations.[36] The yield of **12** was increased to 64 % using dried benzoyl peroxide and LiHMDS as a base. However, a 22 % yield of **14** was still isolated. Although the yield of desired products was not excellent, removal of the chiral auxiliary was investigated.

Treatment of **12** with sodium ethoxide in dry THF produced ethyl mandelate **15** in 88 % yield. Comparison of the optical rotation of the product with the literature value [113] showed that ~18 % of the undesired stereoisomer was formed either during oxidation or ethanolysis.

Further efforts using benzoyl peroxide were abandoned because of the low yields and the loss of stereochemical purity during the oxidation or



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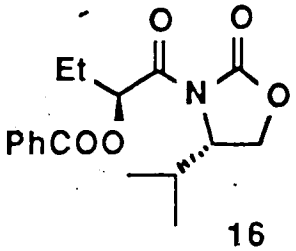
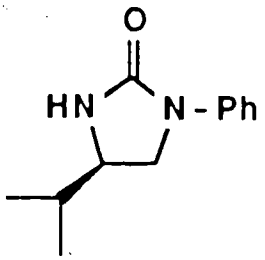


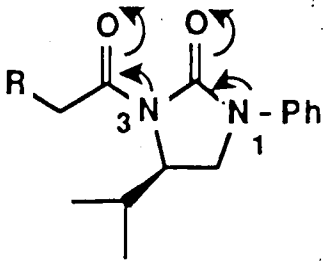
16

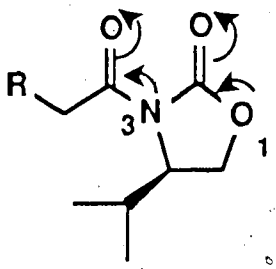
removal of the chiral auxiliary.

Attempts to prepare the magnesium enolates using *tert*- butyl magnesium bromide followed by addition of benzoyl peroxide consistently led to recovery of starting material, even when freshly prepared and titrated reagent was used. Interestingly, attempts to oxidise the lithium or potassium enolate with *tert*- butyl peroxybenzoate also resulted in recovery of starting materials. This may be due to the inability of the reagent bearing a *tert*- butyl group to reach the sterically crowded reaction site.

Use of an imidazolidinone chiral auxiliary was considered in the hope that the corresponding carboximide derivative would not be prone to advantitious cleavage of the side chain. It was expected that the higher contribution of the lone pair of the nitrogen 1 to the imide resonance in the derivatives of imidazolidinone relative to that of oxygen 1 in derivatives of oxazolidinones **5** and **6** might stabilise the compound against possible cleavage.

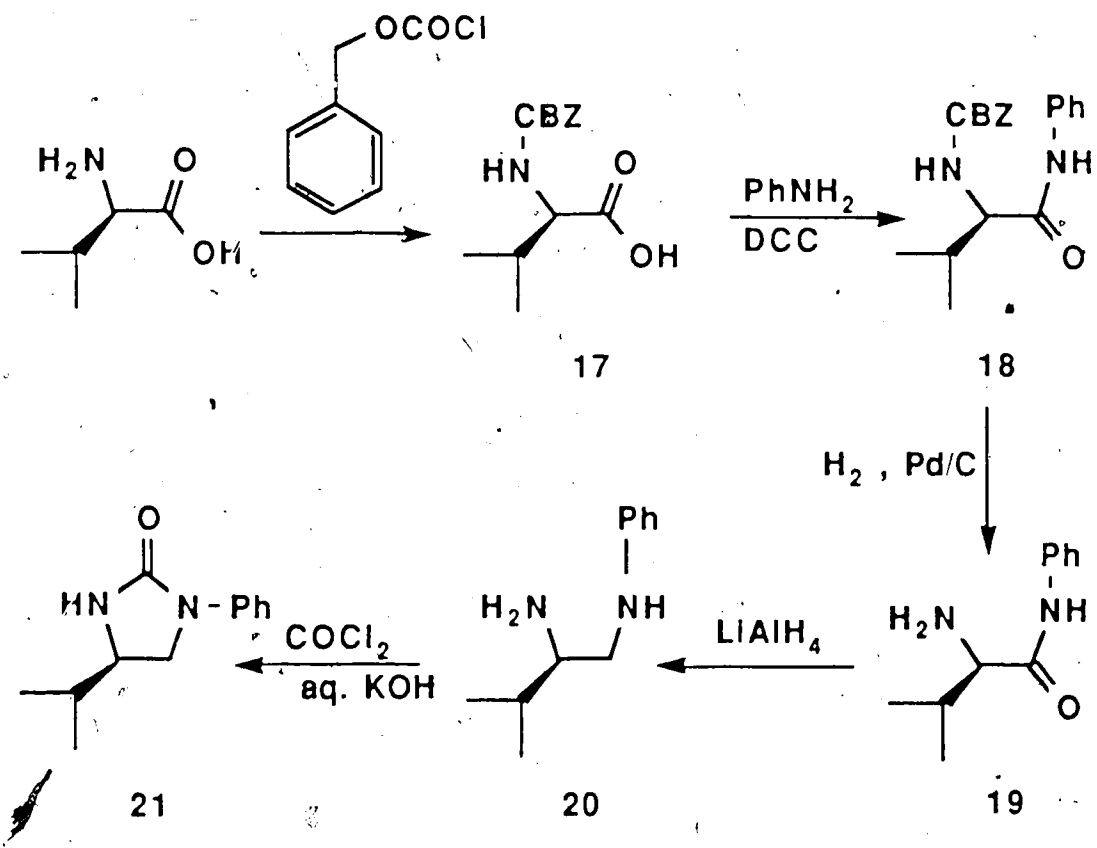






The imidazolidinone auxiliary could be prepared using a simple sequence of steps from D-valine as shown in scheme 6. Reaction [114] of D-valine with benzyl chloroformate under basic conditions gave *N* - CBZ D-valine (17). Condensation [115-117] of **17** with aniline using dicyclohexylcarbodiimide (DCC) gave amide **18** in 62 % yield. Hydrogenolysis [118] of **18** gave amine **19** (87 % yield) which was reduced [119] with lithium aluminium hydride to afford diamine **20** in 56 % yield. Reaction [111, 120] of **20** with phosgene under basic conditions produced **21** (87 % yield).

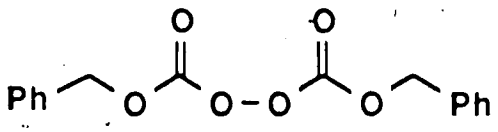
Scheme 6.



Unfortunately all attempts to acylate **21** using bases such as butyllithium, pyridine, triethylamine and sodium hydride failed to give the desired

acylated product. Starting imidazolidinone **21** was consistently recovered. Although the TLC (thin layer chromatogram) of the reaction mixture suggested appearance of a new product, two dimensional TLC as well as tailing of the spot indicated that the compound formed was decomposing to **21**. This may be due to acylation on the imide oxygen to give *O*- acylated product, which decomposes on silica gel and during aqueous work up to give **21**. It was concluded that this chiral auxiliary was not useful for our purpose.

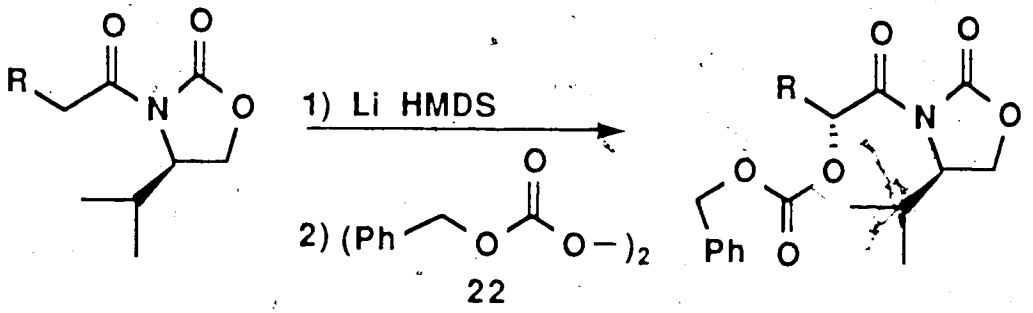
In continuation of our study using oxazolidinone carboximides, dibenzyl peroxydicarbonate (**22**) was examined for oxidation of enolates, since it is a stable crystalline solid and can be prepared from hydrogen peroxide in one step.[121] Previous investigations by Schank[46] using peroxydicarbonates for oxidation of enolates of β dicarbonyl compounds had resulted in only low yields of desired products. Over-oxidation of the desired product is often a problem if the product bears an α-hydrogen. This difficulty can be partially overcome by using enolates derived from enamine derivatives of β-dicarbonyl compounds.[47, 48] Over-oxidation of the initial product is not expected to be a problem with the far less acidic monocarbonyl compounds. However, the oxidation of enolates of monocarbonyl compounds using peroxydicarbonates had not been reported.



22

The reagent **22** can be prepared from commercially available, inexpensive benzyl chloroformate and 30 % aq. hydrogen peroxide under basic conditions.[121] It is a stable, nonhygroscopic, crystalline solid. The enolates of carboximides **7 - 10** generated at -78 °C using lithium bis(trimethylsilyl) amide in dry THF react with dibenzyl peroxydicarbonate **22** at -78 °C, and produce the corresponding oxidised products **23 - 26** in good yields after acidic workup. (scheme 7).

Scheme 7.



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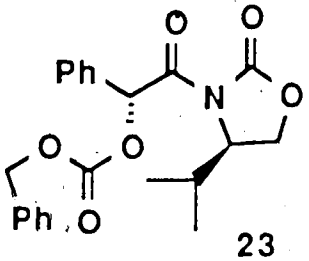

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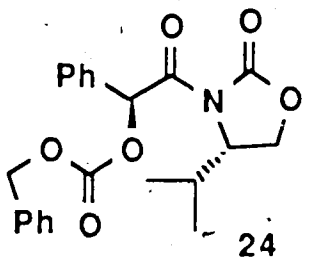

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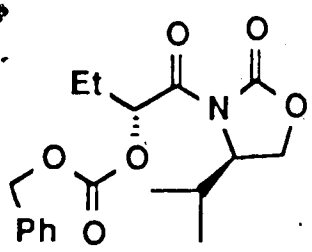

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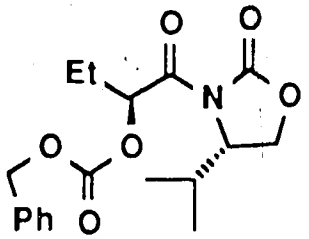
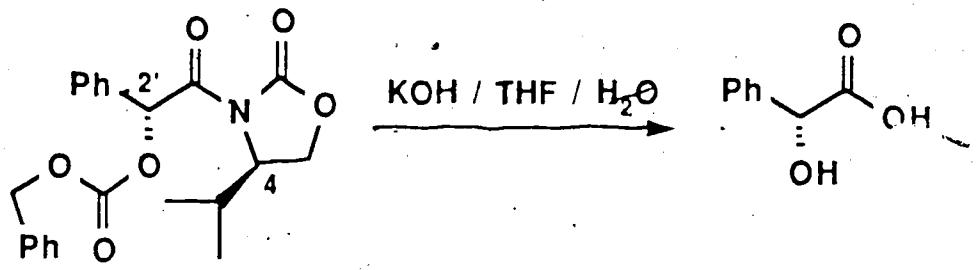


26

Since the oxidation using dibenzyl peroxydicarbonate **22** seemed promising, the diastereoselectivity of the reaction was examined.

Hydrolysis of **23** using aqueous potassium hydroxide followed by purification using ion-exchange chromatography gave *R*-mandelic acid **(27)** (scheme 8).

Scheme 8.

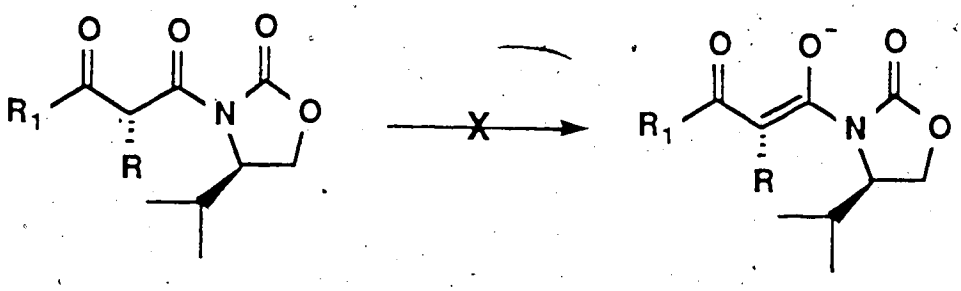


23 **27**

Comparison of the optical rotation of **27** with the literature value [122] showed that 8 % loss of stereochemical purity occurred either during oxidation or hydrolysis. The ^1H NMR spectra of **23** and its 2' diastereomer **28** are expected to be different. However, the spectrum of the product of the oxidation showed only one set of peaks, suggesting that only one diastereomer (2' *R*, 4 *R*) was present in the sample. In order to observe compound **28**, the 2'*S*, 4 *R* diastereomer of **23**, epimerisation of the 2' center in **23** was attempted using triethylamine or LDA as base. However, no difference in the spectra or HPLC behavior of **23** and the product of the attempted epimerisation reactions could be observed. These observations are consistent with those of Evans [107] for oxazolidinone carboximides bearing a 2' acyl group. Evans found that the epimerisation at the 2' center does not occur under mildly acidic conditions or upon treatment with pyridine (scheme 9). Apparently, the compounds

are difficult to enolise because of the strong A (1,3) steric interactions that would result between either acyl or alkyl substituent and imide nitrogen substituents associated with the auxiliary if an enol is formed.

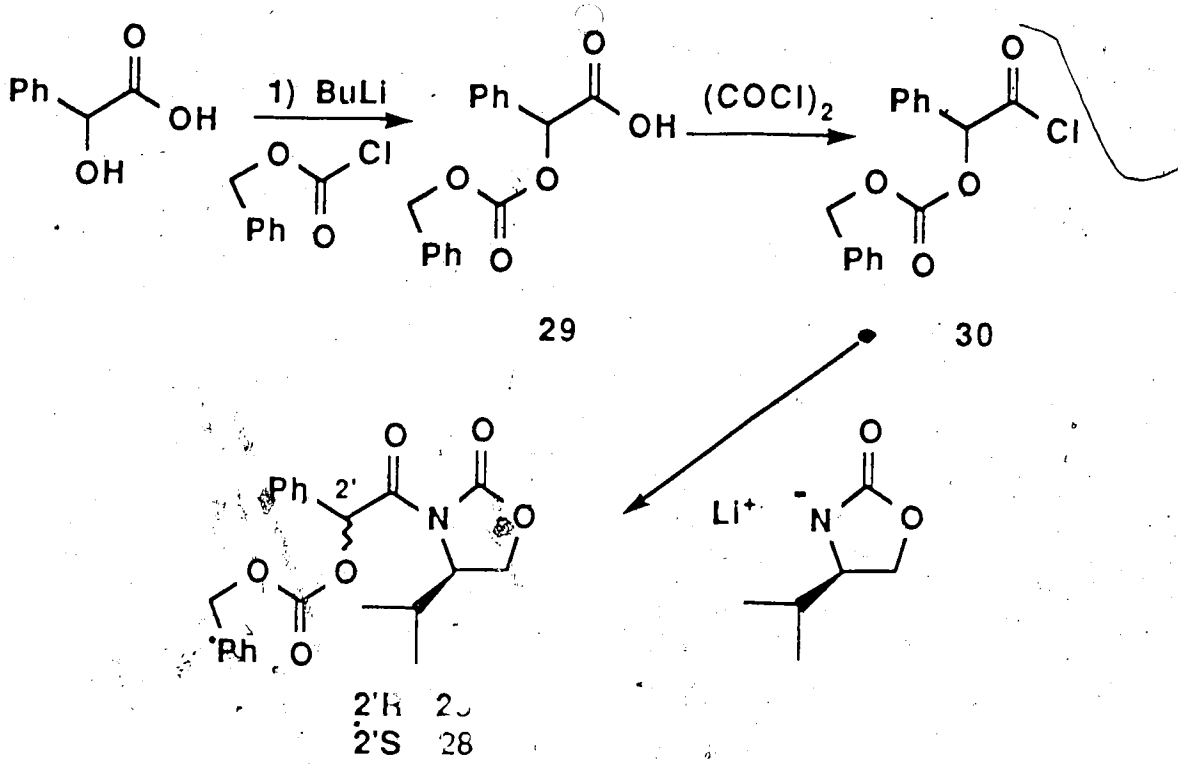
Scheme 9.



Since the ^{1}H NMR and HPLC experiments are not definitive with a single isomer, an independent synthesis of mixture of **23** and its diastereomer **28** from racemic mandelic acid was completed (Scheme 10).

Reaction of racemic mandelic acid with two equivalents of butyllithium and treatment of the dianion formed with benzyl chloroformate gave *O*-CBZ mandelic acid (**29**).[123] Compound **29** was treated with oxalyl chloride to give acid chloride **30** which was not isolated, but treated directly with the anion of **5**. The product of this reaction was identical to **23** by TLC. However, the two diastereomers **23** and **28** can be clearly seen by ^{1}H NMR due to the differences in the chemical shifts of the 2' H and *iso*-propyl methyl signals. The two diastereomers can also be separated by HPLC. Since ^{1}H NMR and HPLC analysis of **23** prepared by oxidation do not show detectable amounts of **28**, it can be concluded that the original oxidation of **7** to **23** has proceeded with > 99 % diastereoselectivity. This also indicates that the loss of stereochemical purity has occurred during the removal of the chiral auxiliary.

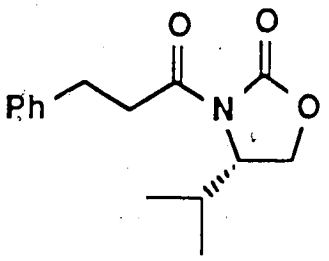
Scheme 10.



During the course of our study, Evans reported a method to remove the chiral auxiliary without loss of stereochemical purity from the corresponding 2' hydroxy derivatives, using magnesium methoxide.[90] Since the carbobenzyloxy group can be cleaved by hydrogenolysis to give the 2' hydroxy derivatives,[118] further efforts to develop a method to remove the chiral auxiliary were discontinued.

The oxidations of carboximides **31**, **32**, and **33** were also studied. The hydrocinnamoyl derivative **31** and the *iso* -valeryl derivative **32** can be oxidised in 81 % and 46 % yield respectively. In the case of **31**, 6 % of the 2'*R* diastereomer of **34** can be detected by ^{1}H NMR. The oxidation of **32** gave a complex mixture (TLC), but the product **35** can be crystallised

from the crude mixture. Attempts to oxidise **33** resulted in very complex mixtures. Table 1 summarises the results of the oxidation of carboximides.



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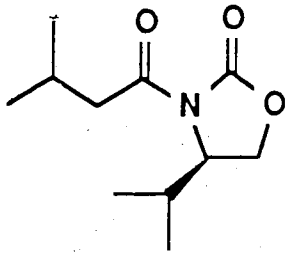

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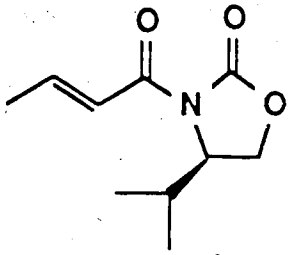

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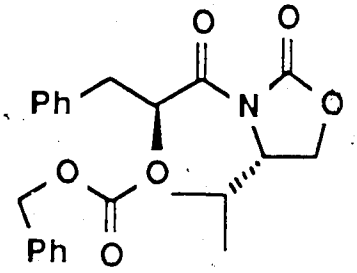

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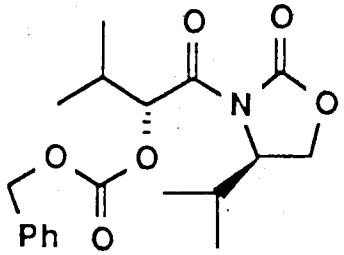
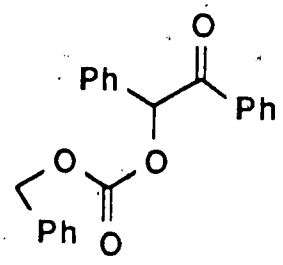


35

Table 1: Oxidation of chiral enolates

Oxazolidinone carboximide	Product	Yield %	Diastereomeric purity %
7	23	82	> 99
8	24	61	> 99
9	25	87	> 98
10	26	89	> 98
31	34	81	94
32	35	46	> 98

The oxidation of simple enolates generated from ketones and esters with dibenzyl peroxydicarbonate **(22)** proved to be unexpectedly difficult. Low yields and complex products resulted in many cases (table 2). 1,2-Diphenylethanone could be oxidised in only 8 % yield to **36** using lithium bis(trimethylsilyl)amide as a base. Ethyl phenylacetate produced a 29 % yield of **37** using KHMDS as a base. Oxidation of the potassium enolate of valerophenone, produced by employing KHMDS as a base, gave a 46 % yield of **38**. Ethyl benzoylacetate, which is difficult to oxidise using MoOPH or phenylsulfonyl oxaziridine, could be oxidised to **39** in 45 % yield (52 % based on recovery of the starting material) using **22**.



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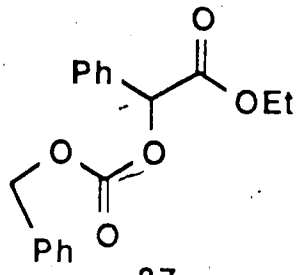

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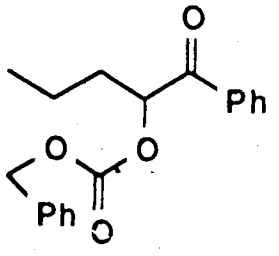

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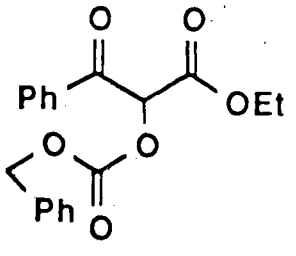
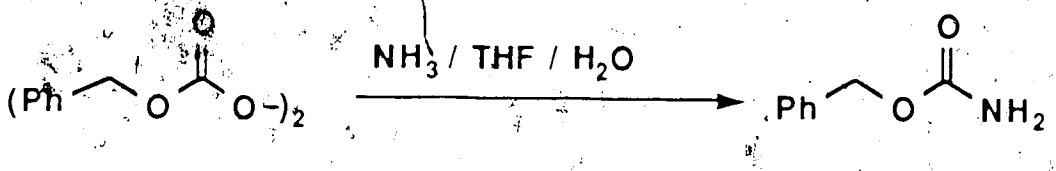


39

Davis and co-workers have reported that lower yields result in phenyl sulfonyloxaziridine oxidations using LDA as a base because the

amine generated in the reaction mixture effectively competes with the enolates for the reagent.[36] This may be one of the factors with the peroxydicarbonate reagent **22**. As expected, the reagent reacts rapidly with ammonia at room temperature to give **40** in high (91 %) yield (scheme 11). It seemed possible that this side reaction could be avoided by using amine free enolates generated fro... silyl enol ethers or by employing more reactive potassium enolates.

Scheme 11.



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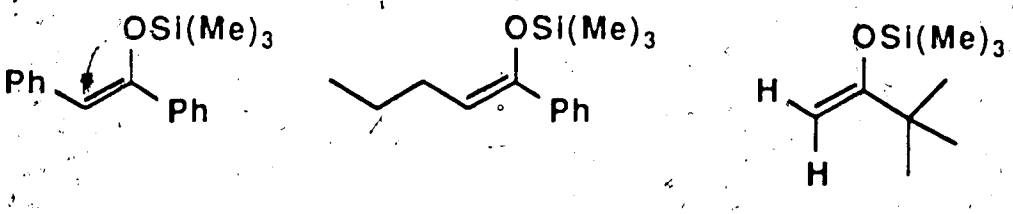
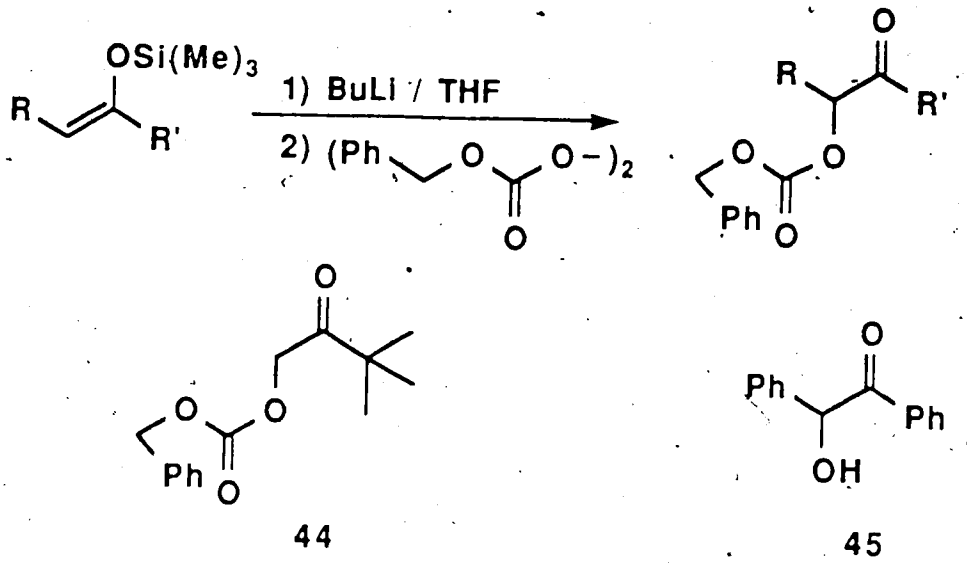
The silyl enol ethers **41**, **42**, and **43** were prepared by a published procedure,[124, 125] the corresponding enolates were generated at 0 °C using butyllithium,[126] and dibenzyl peroxydicarbonate **22** was added at 0 °C to give improved yields of the desired products (scheme 12). The oxidation of **43** gave **44** in 62 % yield. Silyl enol ethers **41** and **42** could be oxidised to give **36** and **38** in 66 % and 36 % yields, respectively.



41 **42** **43**

Scheme 12.



44 45

A remarkable improvement in the yield (an increase from 8 % to 71 %) was obtained in the case of 1,2-diphenylethanone by substituting $KN(Me_3Si)_2$ [127] for $LiN(Me_3Si)_2$. However, the oxidation of titanium or tin enolates[126, 128, 129] generated from **41** gave only low yields of benzoin **45**. Table 2 shows the summary of the results obtained in the study of oxidation of enolates.

In summary, dibenzyl peroxydicarbonate (**22**) is an easily-prepared and stable reagent which oxidises a variety of enolates to benzyl carbonates of the corresponding α-hydroxy carbonyl compounds. Chiral enolates of oxazolidinone carboximides are oxidised by **22** in moderate to high yields with very good diastereoselectivity (≥ 94:6) using $LiN(Me_3Si)_2$ at -78 °C in THF. With simpler enolates of ketones and esters, the yields are usually lower (45-71 %) and depend on the method of enolate formation. Potassium enolates (formed with $KN(Me_3Si)_2$) or amine-free

Table 2: Oxidation of achiral enolates

Compound	Base / reagent	Product	Yield %
1,2-diphenylethanone			
	LiHMDS	36	8
	KHMDS	36	71
Ethyl phenylacetate	KHMDS	37	29
Valerophenone	KHMDS	38	46
Ethyl benzoylacetate	LiHMDS	39	45 (52)
41	BuLi	36	66
	$TiCl_4$	45	33
	$SnCl_4$	45	19
42	BuLi	38	36
43	BuLi	44	62

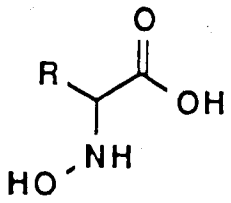
lithium enolates (formed from silyl enol ethers and butyllithium) give the best results. Although the oxidations with phenyl sulfonyl oxaziridines [35, 36] generally give better yields in case of simple enolates, the method using 22 should allow easy access to oxygen-18 labeled compounds. The introduction of an α-hydroxy function as a protected benzyl carbonate ester may be advantageous in synthetic sequences that require protection of this moiety. With a method for stereospecific preparation of 2 available, the transformation of 2 to amino acid analogs such as α-*N*-hydroxyamino, α-oxyamino and α-hydrazino acids was studied (chapter 2).

Chapter 2

Studies on Preparation of α-*N*-Hydroxyamino, α-Oxyamino, and α-Hydrazino Acids.

I. Introduction

Amino acids are important metabolites found in all organisms and play vital roles in many biological processes. The structurally related α-*N*-hydroxyamino acids **46**, α-oxyamino acids **47**, and α-hydrazino acids **48**, in many cases, are strong inhibitors of enzymes that metabolise the corresponding amino acids, and show a variety of biological effects. Hence efficient methods for their stereospecific synthesis are highly desirable.



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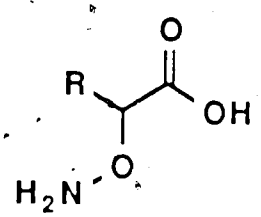

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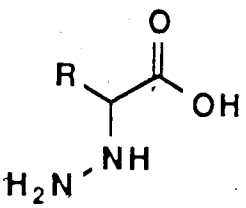

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The α-*N*-hydroxyamino acids **46** are components of hydroxamate antibiotics, tumor inhibitors, and siderophores.[130 - 135] These types of compounds are also intermediates in the biosynthesis of cyanogenic glucosides in plants[136 - 140] and insects.[141] *N*-Hydroxy-L-glutamic acid is a irreversible inhibitor of the pyridoxal phosphate (PLP) dependent enzymes glutamate decarboxylase and glutamate alanine transaminase.[142] Work in our laboratories has shown that *N*-hydroxy analogs of diaminopimelic acid inhibit *meso* diaminopimelate decarboxylase.[143]

The α-oxyamino acids **47** display a similar variety of biological effects. Small peptides containing the oxyamino acids show antibacterial activity against *E. coli*,[144, 145,146] *Staphylococcus aureus*,[144,145] and

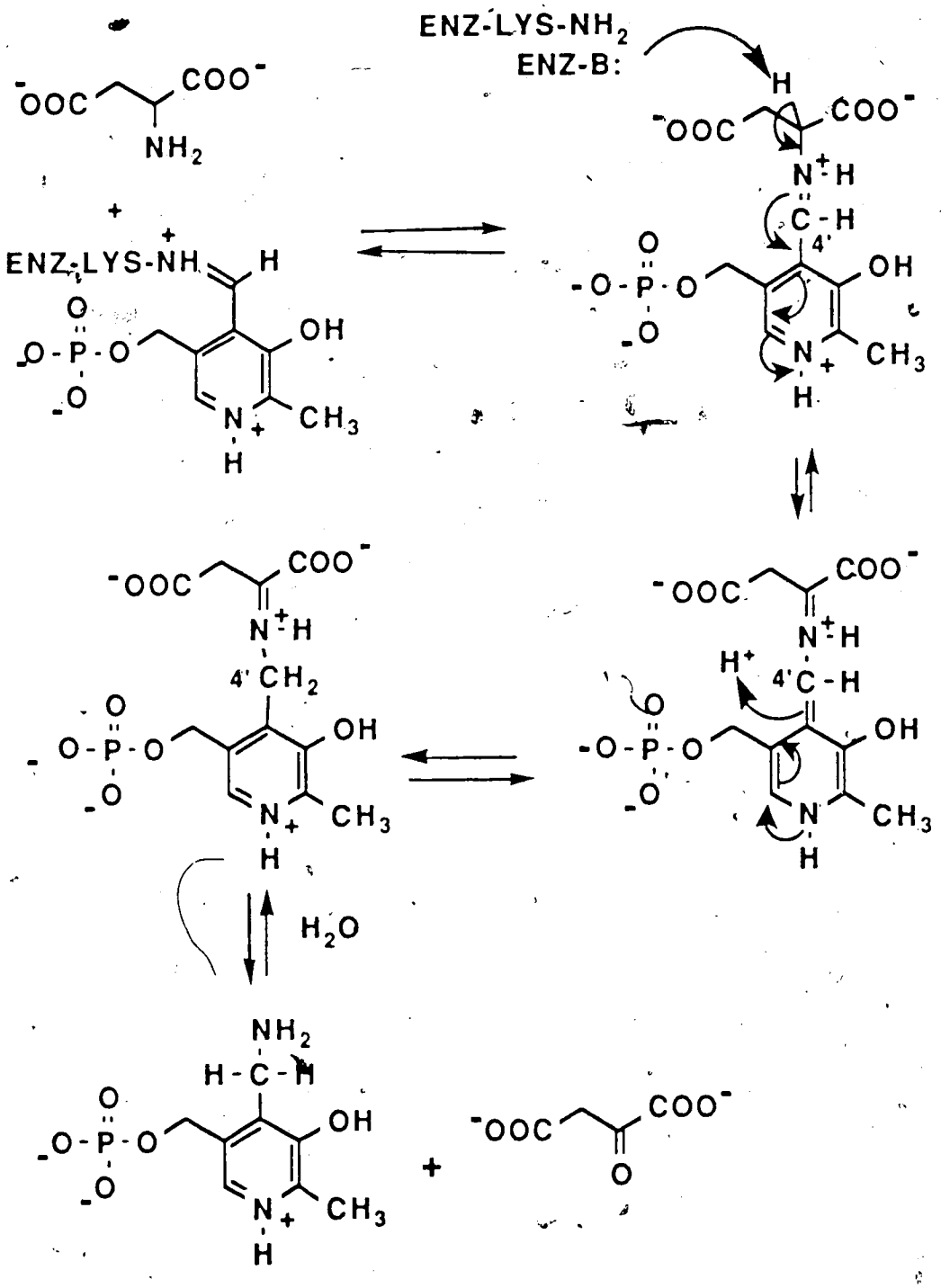
Salmonella dublin.[146] α-Oxyamino β-phenylpropanoic acid induces m-RNA activity and synthesis of phenylalanine ammonia lyase (PAL).[147, 148] The compound also inhibits phytoalexin accumulation in soybeans,[149] causes inhibition of anthocyanine accumulation in *Dacus carota* L.,[150] and is known to inhibit lignin formation.[151] α-D-Oxyaminosuccinic acid is a component of the antibiotic malioxamycin.[152] α-Oxyaminoacetate inhibits ethanol oxidation at low concentrations in isolated hepatocytes, while ethanol oxidation is stimulated at high concentrations.[153] α-Oxyamino butyric and α-oxyamino capronic acids cause convulsions, while α-oxyamino propionic and α-oxyamino *iso* -valeric acids cause muscle relaxation in mice.[154] α-Oxyamino acids have been shown to be inhibitors of ethylene production in plants.[155] Interestingly, spray application of α-oxyamino acids has been used to increase sugar content in sugar cane and in sugar sorghum.[156]

The α-hydrazino acids **48** inhibit pyridoxal phosphate (PLP) dependent enzymes such as histidine decarboxylase,[157 - 159] aspartate aminotransferase,[160 - 163] diaminopimelate decarboxylase,[143] ornithine decarboxylase,[164 - 167] ornithine keto-acid aminotransferase,[165] dopa decarboxylase,[168] and aromatic amino acid decarboxylase.[169] α-Hydrazino β-phenylpropanoic acid inhibits phenylalanine ammonia lyase (PAL).[170 - 172] The α-hydrazino acids show a variety of physiological effects due to their ability to interfere with certain biological reactions. Some of these effects are: production of histidinemia in rats,[173] inhibition of cleavage in fertilised sea urchin eggs,[174] reduction of ethylene production in mung beans and apples,[155] and reduction of renal histamine

concentration in diabetic rats.[175] The α-hydrazino acids and small peptides containing the them display antibacterial activity against *Azotobacter* sp 211 ,[176] *E. coli* ,[176, 144 -145] *Pseudomonas fluorescens*, [177] *Corynebacterium xerosis*,[176] *Bacillus megaterium*,[143, 176] *Bacillus subtilis* [143, 176] and *Salmonella dublin*.[145]

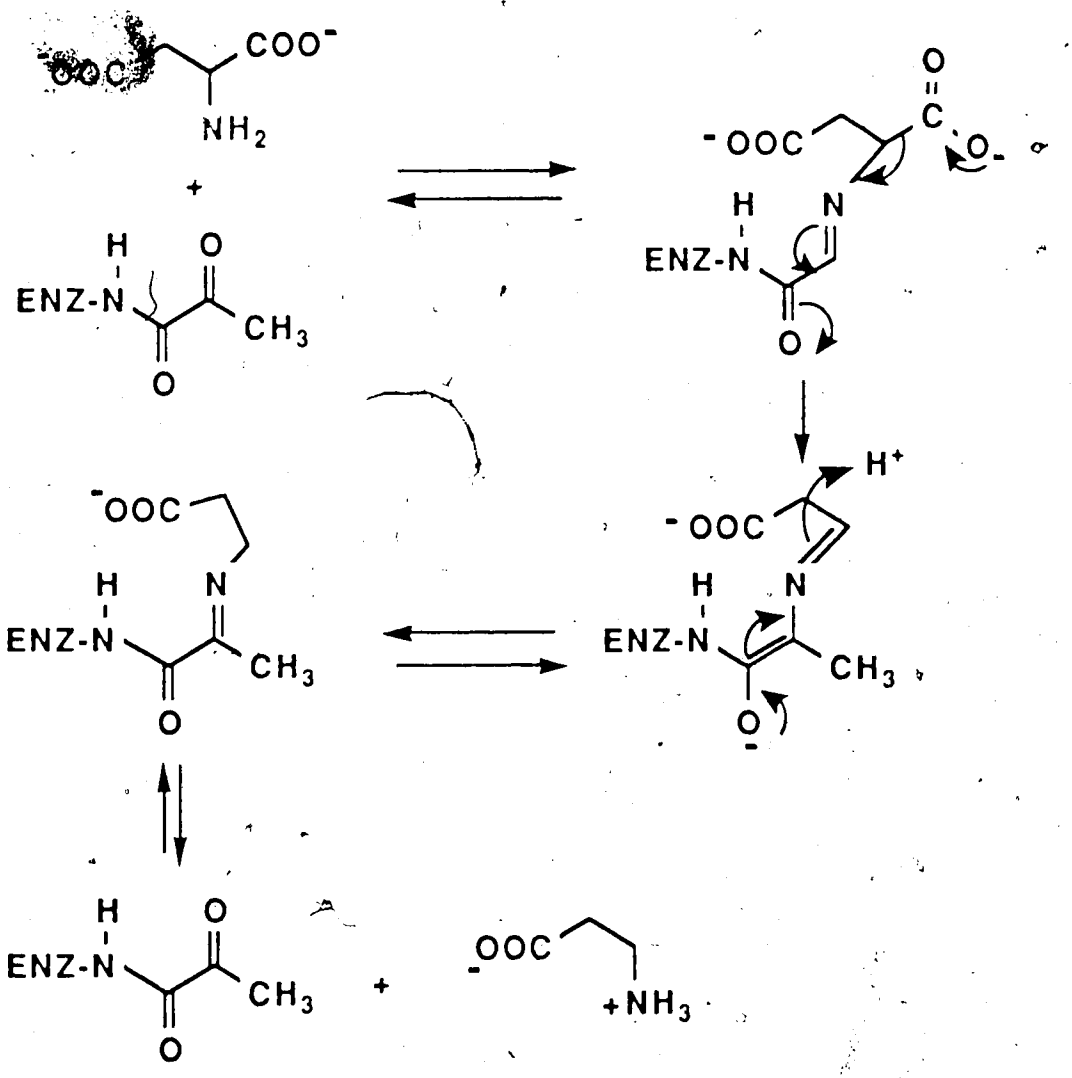
The physiological effects in most cases are probably due to inhibition of key amino acid metabolising enzymes. Many of the enzymes that are susceptible to inhibition by these compounds use either pyridoxal phosphate (PLP) or pyruvate as a cofactor. Mechanisms of catalysis by PLP dependent enzymes are well understood.[177 - 181] A typical PLP mechanism is that of aspartate aminotransferase, [illegible]. The enzyme catalyses the reaction in two discrete stages. Initially, pyridoxal phosphate is bound as an imine at the ε-amino group of a lysine residue of the enzyme active site. In the first stage, transaldimination by aspartate forms the aspartate aldimine, displacing the amine group of the lysine residue. Removal of the proton α to the imine generates a resonance stabilised "carbanionic" intermediate. Reprotonation from the *si* face at C-4' of the cofactor generates the ketimine intermediate. This intermediate is hydrolysed to generate oxaloacetate and pyridoxamine phosphate. In the second stage, exact reversal of the first reaction takes place with pyruvate as the reactant. The protonation of the ketimine intermediate occurs specifically from the *re* face to produce an L-alanine-PLP imine. The alanine is expelled by the ε-amino group of a lysine residue of the enzyme to complete the cycle.

Figure 6. Mechanism of catalysis by PLP dependent aspartate aminotransferase



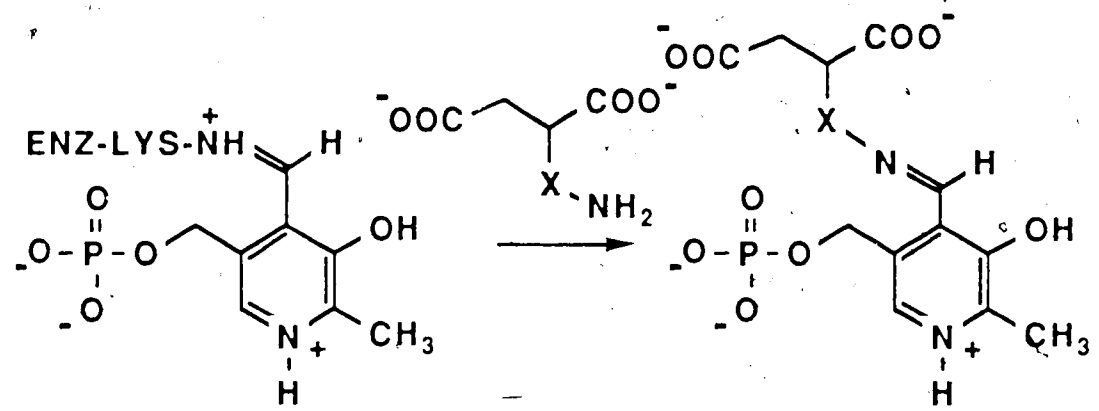
A plausible mechanism of pyruvoyl dependent enzymes is[182] shown in figure 7 for aspartate α-decarboxylase. The aspartate forms an imine with the pyruvate cofactor bound to the enzyme. In a process analogous to PLP catalysis, decarboxylation occurs to generate a resonance stabilised carbanionic intermediate, which is protonated to give the imine of β-alanine. The imine is hydrolysed to regenerate the pyruvate residue and to give β-alanine.

Figure 7. Mechanism of catalysis by pyruvate dependent aspartate α-decarboxylase.



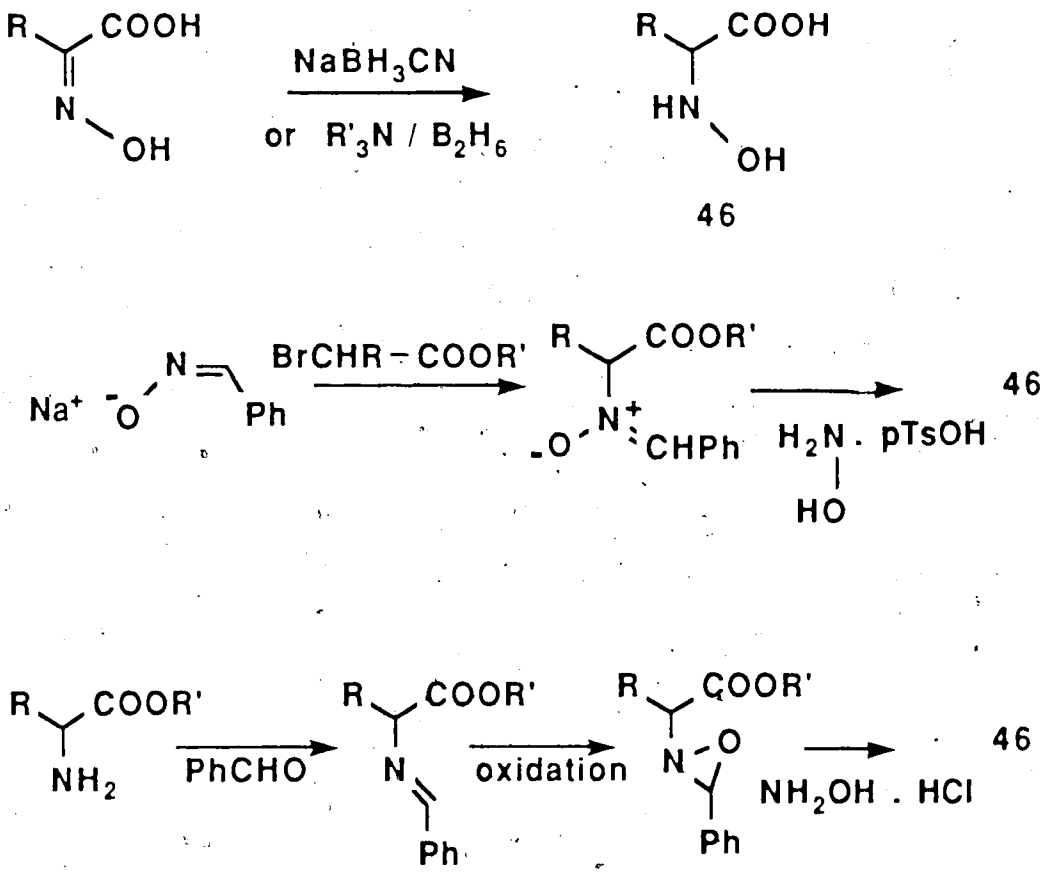
Based on these mechanisms it is possible to postulate the mechanism of inhibition by the α-hydrazino, α-oxyamino, and α-*N*-hydroxyamino acids (figure 8). The inhibition probably occurs by the reaction of the carbonyl functionality in pyridoxal phosphate with the primary amino group of the α-hydrazino acid or the oxyamino acid, to generate an imine which is incapable of forming a resonance stabilised intermediate and which may be much more difficult to hydrolyse than an ordinary amine. In the case of *N*-hydroxyamino acids the reaction appears to lead to formation of a stable nitrone.[142] Hence these compounds usually cause irreversible or strong competitive inhibition of the enzyme. The inhibition of pyruvate dependent enzymes probably functions in an analogous fashion.

Figure 8. Inhibition of PLP dependent enzymes by amino acid analogs



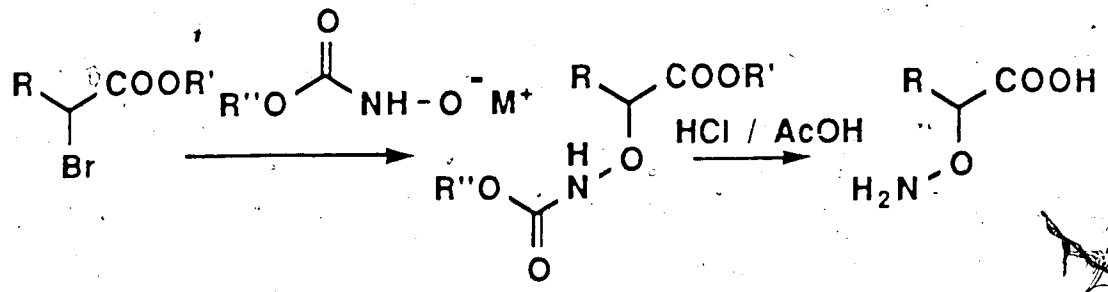
N-Hydroxyamino acids have been prepared in many ways.[183] Reduction of oximes[184 - 188] or hydrolysis of nitrones[189 - 194] are common procedures used to synthesise **46**. Polonski and Chimiak have reported a procedure involving oxidation of imines of benzaldehyde to oxaziridines and treatment with salts of hydroxylamine to produce **46** (figure 9).[195, 196]

Figure 9. Methods for preparation of α-*N*-hydroxyamino acids.



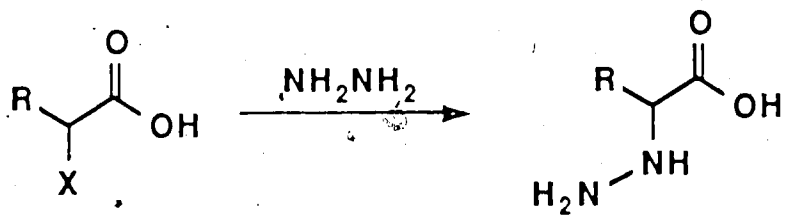
Reaction of alkali metal salts of *N*-hydroxy carbamates with α-bromoacids or α-bromo esters followed by deprotection is the only method reported for the preparation of α-oxyamino acid **47** (figure 10).[152,197]

Figure 10. Method for preparation of α-oxyamino acids.



Several methods for the synthesis of α-hydrazino acids **48** have been reported and are shown in figure 11. The most commonly used method for the preparation of **48** involves the treatment of α-halo acids with hydrazine.[198 - 202] Other less usual approaches are: the reduction of the hydrazones of α-keto acids,[168, 203] reduction of α-diazo esters,[204] nitrosation-reduction of α-amino acids,[206] Hofmann rearrangement of α-ureido acids,[207 -210] and reaction of aldehydes with hydrazine and cyanide in a Strecker synthesis.[210, 211] The utility of these methods is often diminished because of lack of optical purity or low yields. Recently, excellent methods involving reaction of electrophilic aminating reagents with enolates bearing chiral auxiliaries has been reported by the groups of Evans [109], Vederas [212, 213] and Gennari. [214]

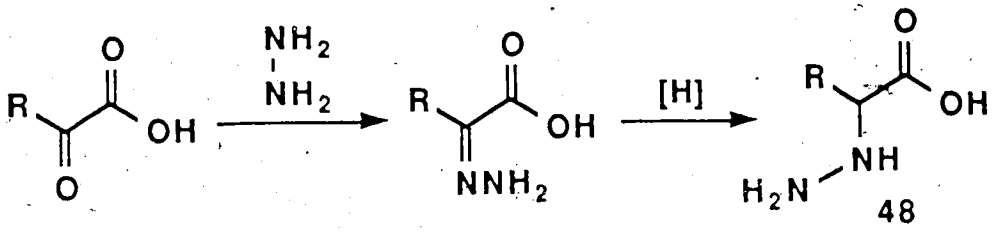
Figure 11. Methods for synthesis of α-hydrazino acids.

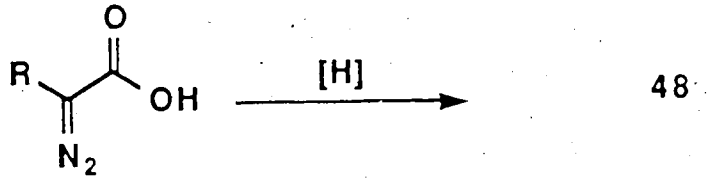


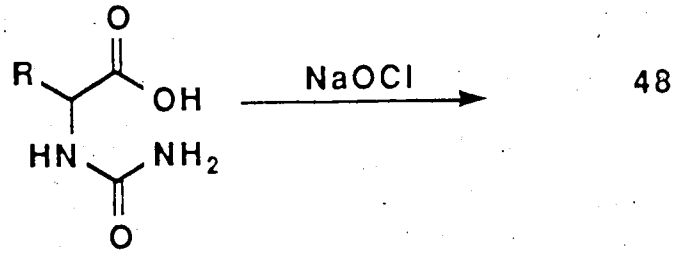
X = Cl, Br

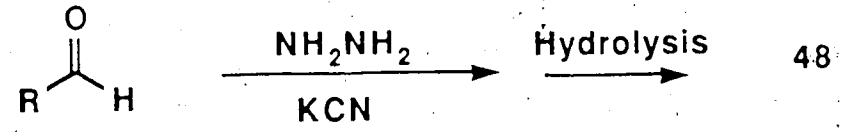
48

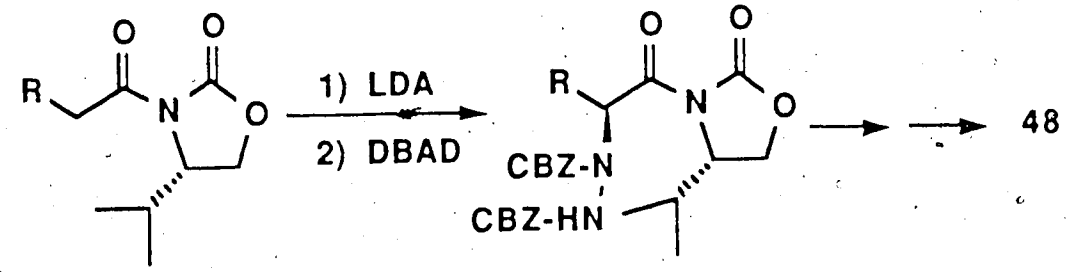
Figure 11. continued...











DBAD = Dibenzyl azodicarboxylate

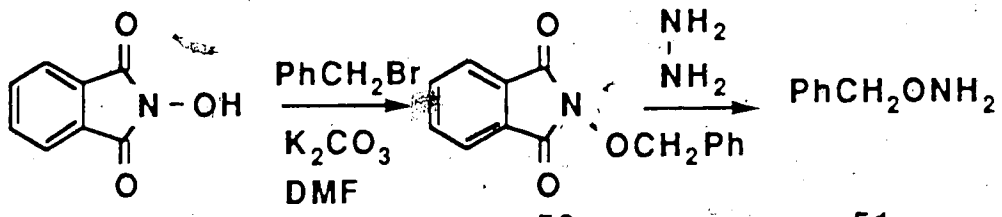
Since chiral α-hydroxy acids are readily available both from nature and by stereospecific synthesis as described previously, we explored methods for the preparation of **46**, **47**, and **48** from these compounds. One of the goals was the preparation of analogs of aspartic acid since two enzymes, aspartate α-decarboxylase and aspartate aminotransferase, were available for enzyme inhibition studies in the laboratories of Dr. Monica Palcic (Food Science Dept., University of Alberta).

II. Results and Discussion

The primary goal was to develop efficient preparations of amino acid analogs **46 - 48** from esters of α-hydroxy acids in high stereochemical purity. A convenient approach appeared to be conversion of the α-hydroxy function to a good leaving group followed by displacement by an appropriate nucleophile. α-Bromo acid derivatives, where bromide is the leaving group, have been used previously. However, disadvantages such as long reaction times, loss of optical purity in preparation of α-*N*-hydroxyamino acids,[183, 191] and use of vigorous conditions in preparation of α-oxyamino acids[197] make this method unattractive. The use of trifluoromethanesulfonate (triflate) derivatives seemed ideal since it was expected to allow fast reactions under mild conditions.[215] After most of our displacement experiments were completed, Ottenheijm reported a similar approach for preparation of α-*N*-hydroxyamino acid derivatives.[215]

For the preparation of α-*N*-hydroxyamino acids the nucleophile of choice is *O*-benzylhydroxylamine, which can be prepared in two steps.[216] Reaction of commercially available *N*-hydroxyphthalimide **(49)** with benzyl bromide under basic conditions gave **50** in 74 % yield. Compound **50** was deprotected by hydrazinolysis to give **51** in 87 % yield (scheme 13)

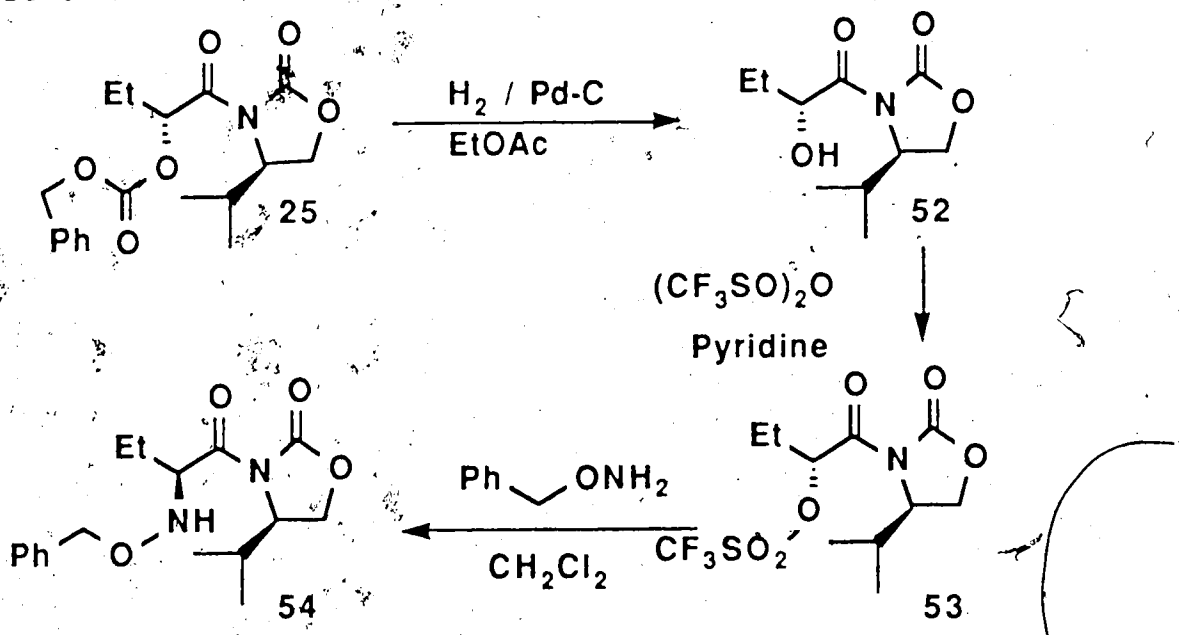
Scheme 13.



49 50 51

In initial studies, oxazolidinone carboximide **25**, available from the work described in chapter 1, was hydrogenolysed in nearly quantitative yield to the 2'-hydroxy compound **52**. Compound **52** was transformed to the corresponding triflate using well precedented reaction conditions (scheme 14).[217, 219]

Scheme 14.



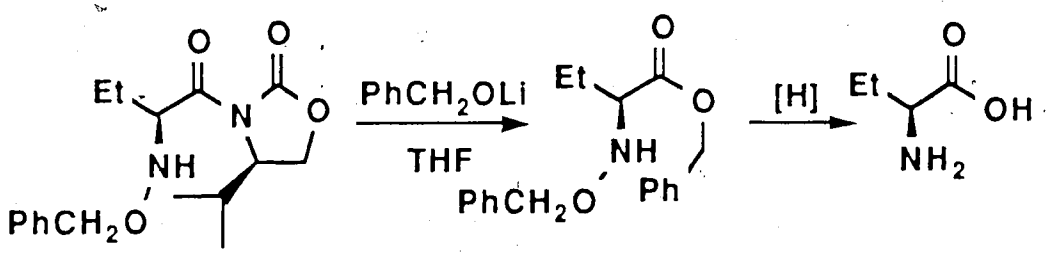
25 52 53 54

Thus, treatment of a solution of **52** and pyridine with trifluoromethanesulfonic anhydride (triflic anhydride) produced triflate **53** in 74 % yield. Reaction of the triflate **53** with *O*-benzyl

hydroxylamine in dichloromethane gave **54** in 54 % yield.

The chiral auxiliary was removed using lithium benzyloxide to afford benzyl ester **55** in 44 % yield. Attempts to prepare the corresponding α-*N*-hydroxyamino acid by selective hydrogenolysis of the *O*- benzyl group using 5 % Pd/C as a catalyst in methanol or methanol-water produced mixtures of α-aminobutyric acid **56**, and the α-*N* -hydroxyamino butyric acid, as indicated by TLC and by ^{1}H NMR of the products. Although the removal of *O* -benzyl groups from these types of compounds is precedented if the nitrogen bears an acyl group,[185] it seems that the *O* -benzyl group can not be selectively hydrogenolysed without cleavage of the nitrogen-oxygen bond if the acyl group is not present. Thus, benzyl ester **55** was converted directly to α-aminobutyric acid (**56**) by hydrogenolysis [118] over 5 % Pd /C (scheme 15).

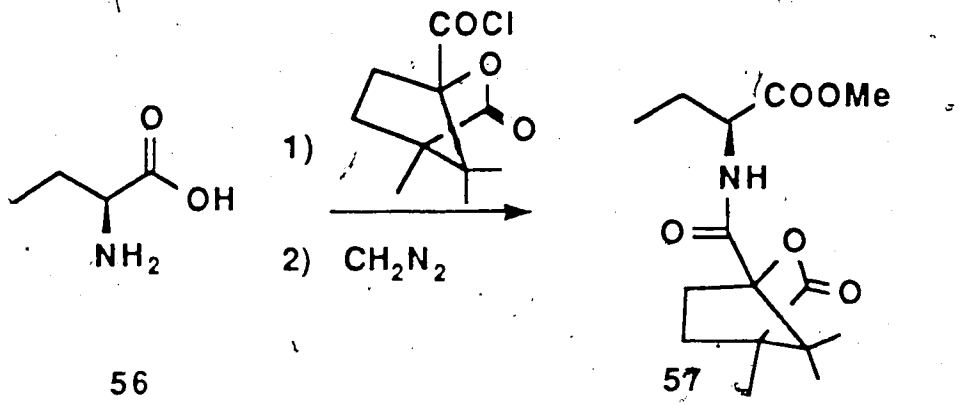
Scheme 15.



54 **55** **56**

The enantiomeric purity of **56** was easily determined by conversion of amino acid **56** to camphanamide methyl ester **57** (scheme 16) since previous work in our laboratories [213, 220, 221] had shown that the reaction of amino acids with (-) camphanic acid chloride proceeds without chiral recognition and that the diastereomeric camphanamide methyl esters can be separated by gas chromatography.

Scheme 16.

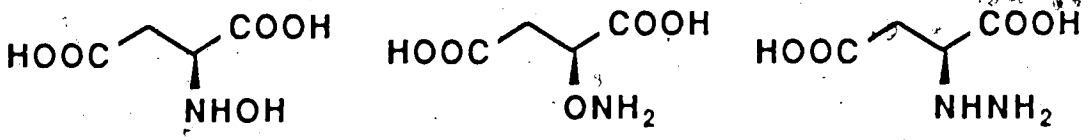


56 57

Gas chromatography of **57** and comparison with standards [221] showed that the major enantiomer had the 2*S* (L) configuration as expected, but showed that 10.0 ± 0.2 % of the 2*R* (D)enantiomer was also present. The loss of stereochemical purity is believed to have occurred during the removal of the chiral auxiliary since our observations (Chapter 1, p 24 - 26) and those of Evans [90] indicate that this is the case for the 2-hydroxy carboximides when basic conditions are used to remove the oxazolidinone moiety.

The next goal was to prepare pure enantiomers of the α-*N*-hydroxyamino, α-oxyamino and α-hydrazino analogs of aspartic acid .

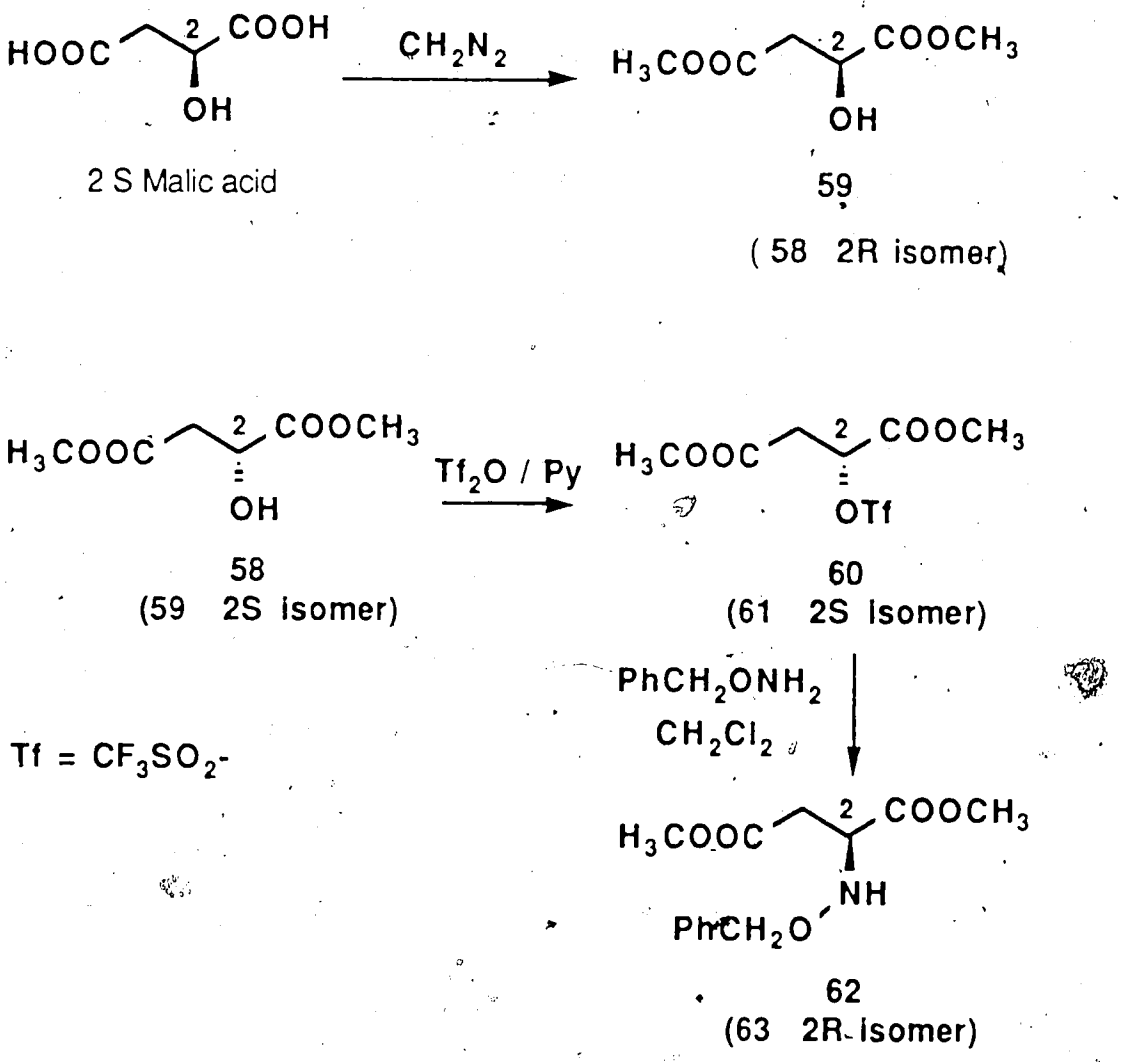
Synthetic goals.



Commercially available *R* and *S* malic acids were easily converted to the methyl esters **58** and **59** respectively, in nearly quantitative yield. The

esters were transformed to the trifluoromethanesulfonates **60** and **61** in good (~ 90 %) yield (scheme 17). The trifluoromethanesulfonyl group was displaced by *O*-benzyl hydroxylamine to give the protected *N*-hydroxyamino acid derivatives **62** and **63**,[215] in > 85 % yield.

Scheme 17.

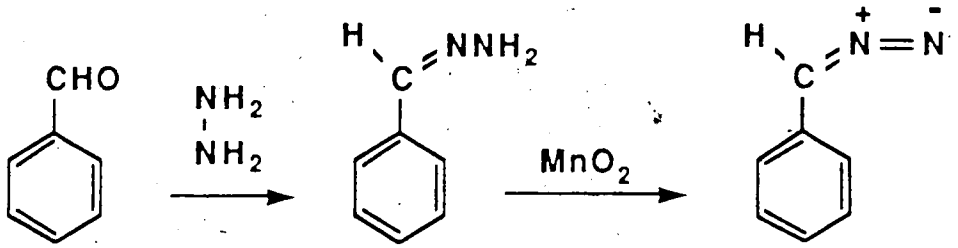


Unfortunately, all attempts to deprotect these compounds using reagents such as trimethylsilyl iodide,[222, 223] 5.7 N HCl,[224] trimethylsilyl chloride /

sodium iodide,[225] and boron tribromide [226] gave complex products.

Since benzyl esters can be easily deprotected by hydrogenolysis,[118] in most cases under neutral conditions, use of such esters appeared to be a viable alternative. The benzyl esters of *R* and *S* malic acids were initially prepared using phenyldiazomethane **(64)**.[227, 228] Phenyl diazomethane prepared by oxidation [227] of benzaldehyde hydrazone required purification by distillation, which is a cumbersome and hazardous procedure (scheme 18).

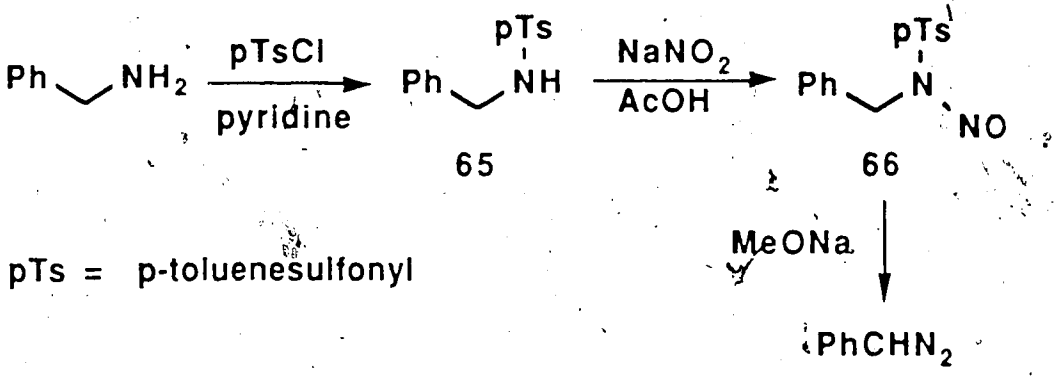
Scheme 18.



64

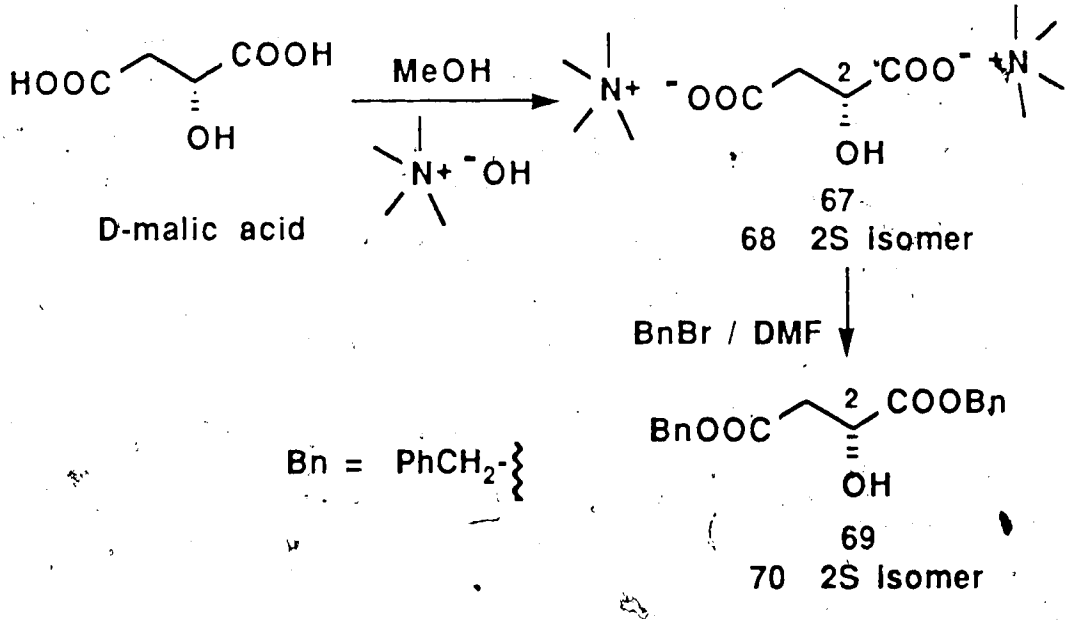
Another procedure reported in the literature that is expected to give phenyl diazomethane [228] that may not need purification involves treatment of *N*-nitroso-*N*-benzyl p-toluenesulfonamide **(66)** with sodium methoxide. Nitrosation of *N*-benzyl p-toluenesulfonamide **(65)** gave compound **66** in 80 % yield . [229] Benzyl esters of satisfactory purity could not be obtained by this procedure without distillation of phenyldiazomethane. (scheme 19).

Scheme 19.



Alkylation of tetramethylammonium carboxylates is an alternative procedure,[230] although it is not clear from the literature if epimerisation occurs in the preparation of the tetramethylammonium salts. The D and L enantiomers of malic acid each reacted with 2 equivalents of tetramethylammonium hydroxide to give the salts 67 and 68, respectively, which were dried and treated with benzyl bromide (scheme 20).

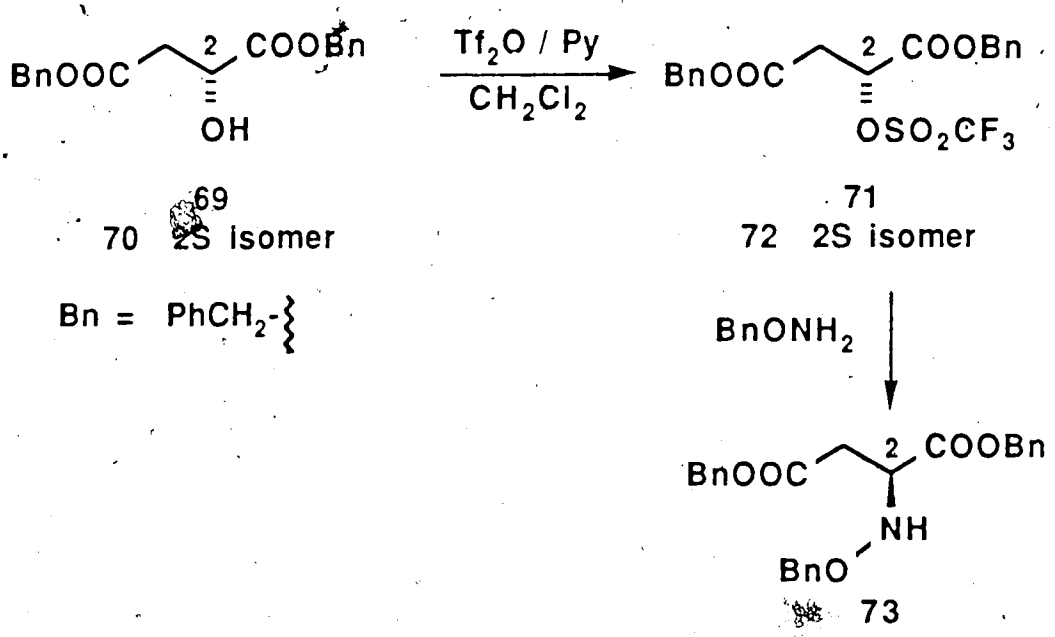
Scheme 20



The benzyl esters[230] were obtained in > 85 % yields and showed comparable optical rotations to the esters prepared by the

phenyldiazomethane method, thereby suggesting that no racemisation has occurred during preparation of the salt. The dibenzyl esters **69** and **70** were transformed to the triflate derivatives **71** and **72**, respectively, in > 85 % yields. Triflate **71** was treated with *O*-benzylhydroxylamine to give substituted product **73** in 66 % yield (scheme 21).[215,231]

Scheme 21.

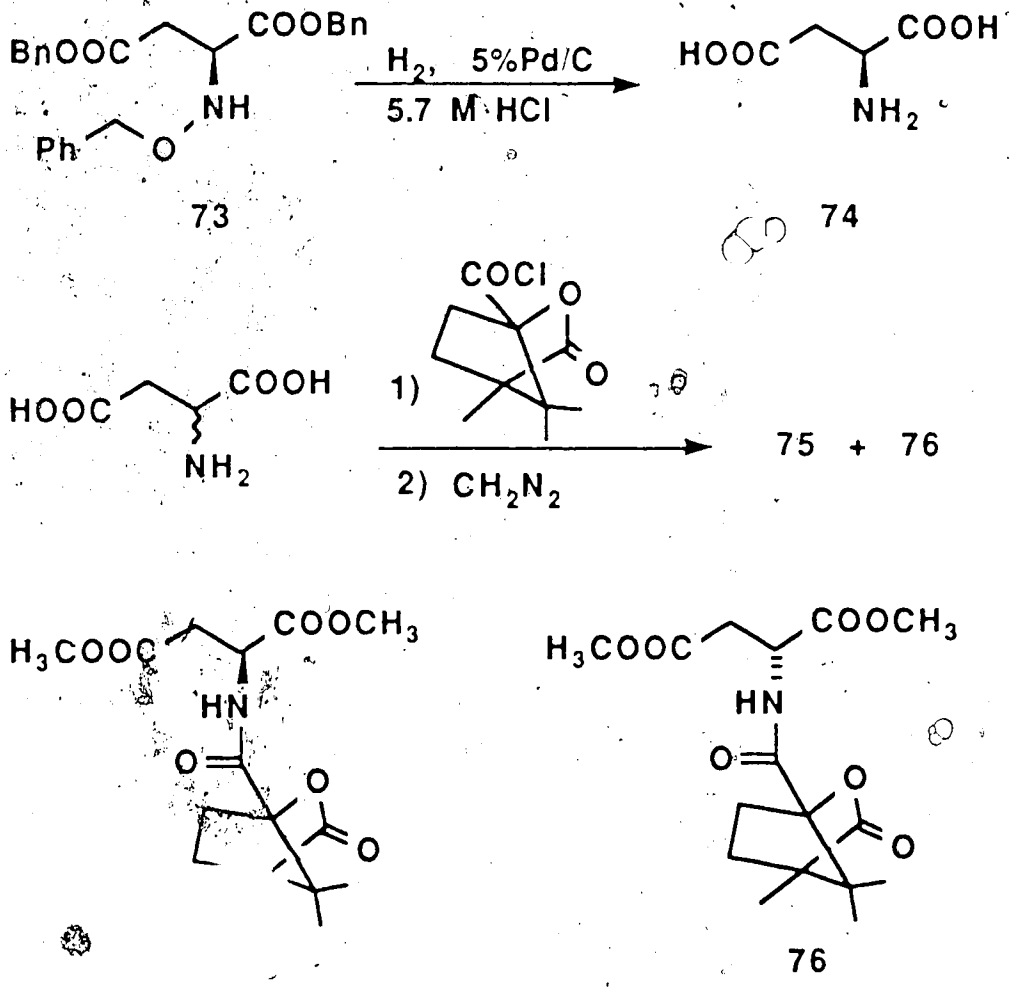


Hydrogenolysis [118] of **73** gave a mixture of aspartic acid and the *N*-hydroxyamino acid as indicated by ^{1}H NMR and by TLC. Attempts to isolate the *N* - hydroxyamino acid from this mixture by ion-exchange chromatography gave aspartic acid and a complex mixture of products. Although the selective hydrogenolysis of this type is well precedented in the literature when the nitrogen is acylated, the results above as well as results of Ottenheijm [184, 215] once again indicate that the hydrogenolysis of the benzyl group without cleavage of nitrogen - oxygen bond is not

possible if the nitrogen is not acylated (cf p 47). Nevertheless, the compound, in principle, can be used for preparation of peptides containing N-hydroxyamino acids.[232, 233]

The stereochemistry of **73** was analysed by conversion to L-aspartic acid **74**, transformation of **74** to its camphanamide dimethylester[213, 220, 221] **75**, and comparison with authentic **75** and a standard mixture of **75** and **76** (the 2*R* diastereomer of compound **75**) (scheme 22).

Scheme 22.

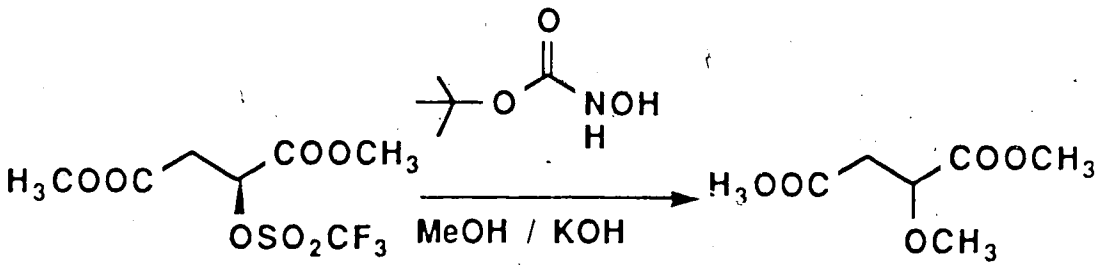


Although the two camphanamide diastereomers showed similar chromatographic behaviour (TLC, GC), they were clearly distinguished by

^{1}H NMR spectra due to the differences in the chemical shifts of the methyl ester protons. The ^{1}H NMR spectrum of the camphanamide methyl ester derived from **74** showed that ~ 4 % of the *R* enantiomer is present, thus indicating that a small loss of stereoselectivity has occurred in the displacement reaction. Since two reports [234, 235] in the literature indicated that *N*-hydroxy aspartic acid is a very unstable compound, and since it had not yet been synthesised, further efforts to prepare this potential enzyme inhibitor were abandoned.

For the preparation of the corresponding oxyamino acid isomers, displacement reactions using the potassium salt of *tert*-butyl-*N*-hydroxy carbamate were investigated.[197] The reaction of triflate **61** using methanol as solvent gave **77** formed by methoxide substitution (scheme 23).

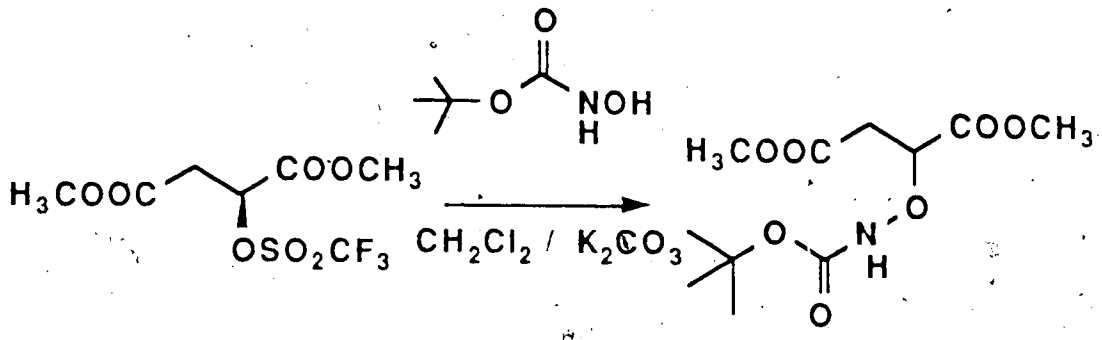
Scheme 23.



61 **77**

A low (26 %) yield of product **78** was obtained after 16 h upon reaction of triflate **61** with *tert*-butyl-*N*-hydroxycarbamate and finely divided K_2CO_3 in dichloromethane (scheme 24).

Scheme 24.

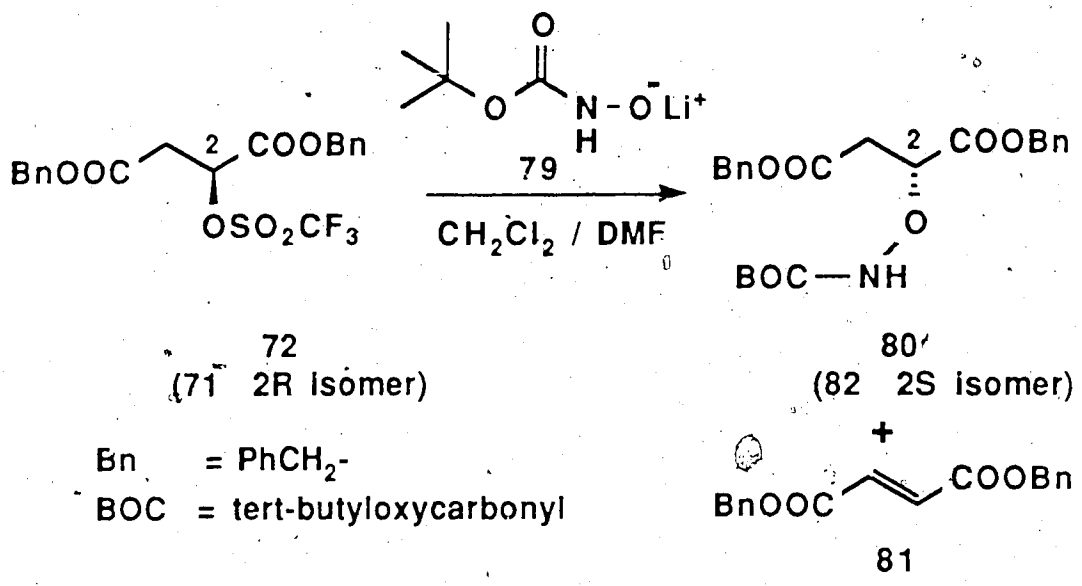


61 78

In the view of the difficulty encountered in deprotection of the ester methyl groups in the case of the *N*-hydroxy derivative (pp 49 - 50), and lower yields in the case of substitution using *tert*-butyl-*N*-hydroxycarbamate as a nucleophile, further work using methyl esters was abandoned in favour of better approaches.

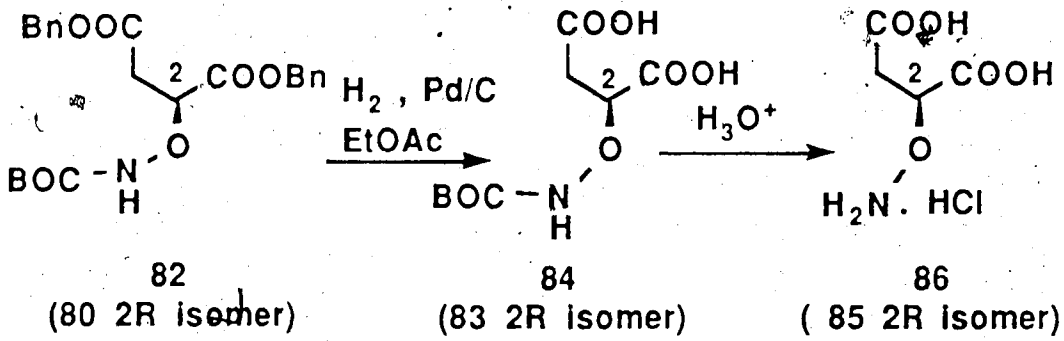
The efforts to prepare the oxyamino acids using benzyl esters proved to be much more rewarding. Triflate **72**, prepared from *S*-malic acid dibenzyl ester in the usual manner, reacts with lithium *tert*-butyl-*N*-hydroxycarbamate (**79**) in 1:3 dichloromethane / DMF to give substituted product **80** in moderate (40 %) yield. Elimination was a major side reaction, leading to the formation of dibenzyl fumarate (**81**) (24 %). A small amount (9 %) of the starting material was also isolated. The yield and the stereoselectivity (*vide infra*) were improved in case of *R* triflate **71** to give **82** (62 %) when the reaction was done at 0 °C. However, the elimination product **81** was still isolated in 16 % yield (scheme 25).

Scheme 25



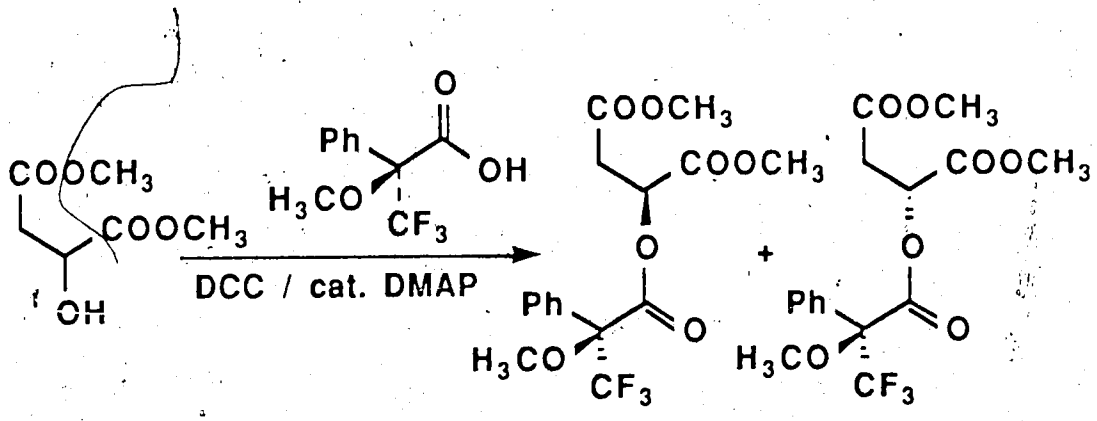
Compounds 80 and 82 were easily hydrogenolyzed [118] to afford the BOC derivatives 83 and 84, respectively, in nearly quantitative yields (≥ 95 %). The compounds 83 and 84 were deprotected using 5.7 N HCl / THF to give the corresponding oxyamino acids [152] 85 and 86, respectively, which were isolated as hydrochloride salts in ≥ 96 % yields (scheme 26). The oxyamino acid hydrochlorides were submitted for enzyme inhibition studies and anti-microbial testing (see Appendix).

Scheme 26.



The stereochemical purities of these compounds were determined as follows. The oxyamino acids were hydrogenolysed to the corresponding malic acids using platinum oxide catalyst. The malic acids were methylated with diazomethane to give dimethyl esters **87** and **88**, respectively. The dimethyl esters **88** and **87** were transformed to the Mosher (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl (MTPA) esters [236, 237] **89** and **90**, using DCC as the coupling reagent.[27, 28] The Mosher esters were separated using gas chromatography (GC) and their stereochemical purities were assessed. The esters were also prepared from a standard mixture of L- malic acid and D-malic acid. The estimations of the percentages of the two enantiomers in the original mixture determined by GC is within ± 0.2 %. The analysis of D oxyamino acid **85** showed 11.8 ± 0.2 % of the L enantiomer was present while the analysis of the L-oxyamino acid **86** showed 3.7 ± 0.2 % of the D enantiomer was present (scheme 27).

Scheme 27.



2R **87**
2S **88**

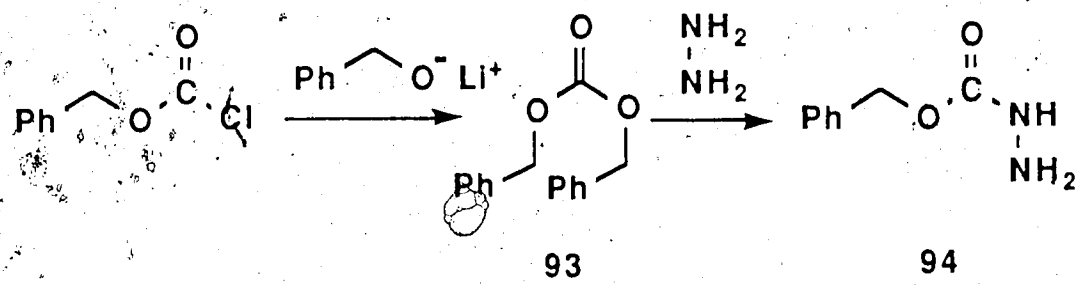
89 **90**

The difference between the enantiomeric ratios for the D and L

oxyamino acids **85** and **86** is believed to be due to the difference in the temperature at which the reactions were done. The lower loss of stereochemical purity in preparation of **86**, in which the reaction was performed at lower temperature (0 °C), is consistant with preceding hypothesis. It is noteworthy that L-oxyaminosuccinate proved to be an extremely potent inhibitor of aspartate aminotransferase (see Appendix).

To prepare the hydrazinosuccinates **(91)** and **(92)** from the triflates **71** and **72**, benzyl carbazate **(94)** [238] was required as a nucleophile. This compound could be prepared in two steps as shown in scheme 28. Treatment of lithium benzyloxide, prepared by the reaction of butyllithium with benzyl alcohol, with carbobenzyloxy (CBZ) chloride gave dibenzyl carbonate **(93)** in good (84 %) yield. Hydrazinolysis of the carbonate produced benzyl carbazate **(94)** (57 %) (scheme 28).

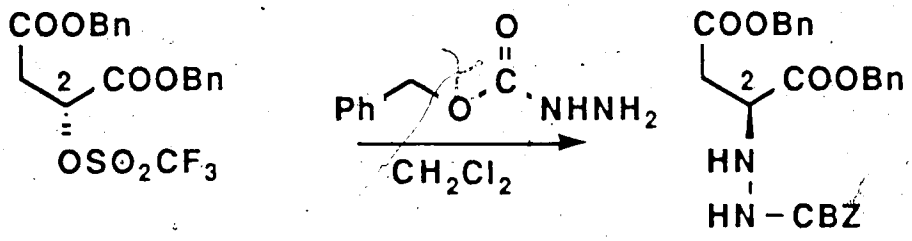
Scheme 28.



93 94

The triflates **71** and **72** reacted with benzyl carbazate **(94)** to produce protected α-hydrazino succinates **95** and **96**, respectively, in ≥ 89 % yield (scheme 29).

Scheme 29.

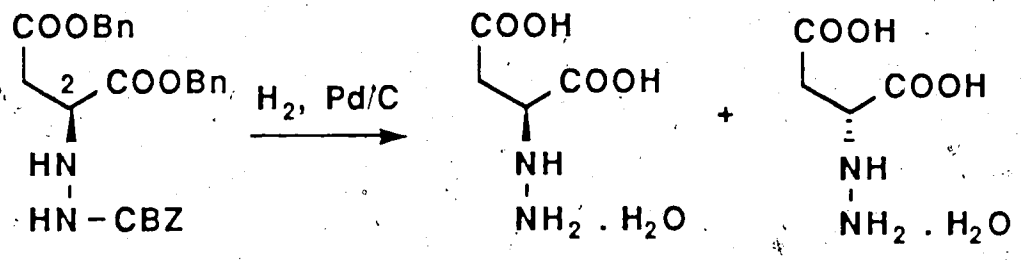


71
72 2S isomer

95
96 2R isomer

Deprotection of **95** and **96** by hydrogenolysis using Pd/C as the catalyst, produced α-hydrazinosuccinates [161, 162] **91** (52 %) and **92** (74 %), respectively, which were recrystallized as hydrates from water/ THF (scheme 30).

Scheme 30.



95
96 2R isomer

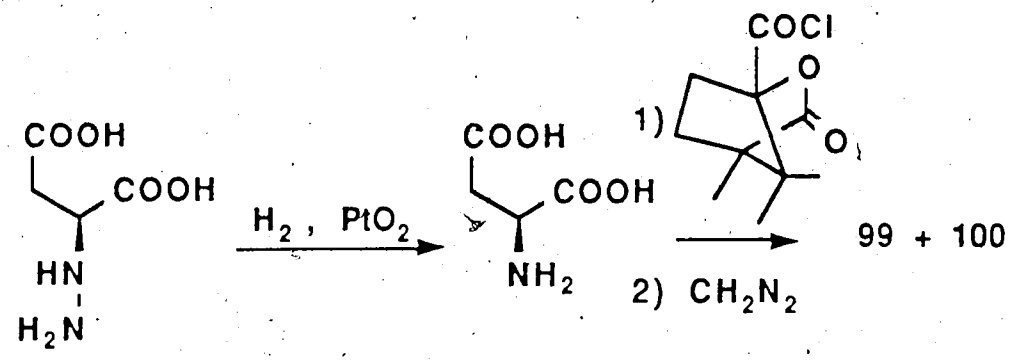
91

92

For the determination of stereochemical purity, the hydrazino succinates were reduced to aspartic acids **97** and **98**, using platinum oxide catalyst. The aspartic acids were converted to the (-) camphanamide dimethyl esters **99** and **100** (scheme 31). Enantiomeric purity was estimated using ^{1}H NMR (400 MHz) since the methyl ester protons of the two diastereomers have different chemical shifts (scheme 31). Standards

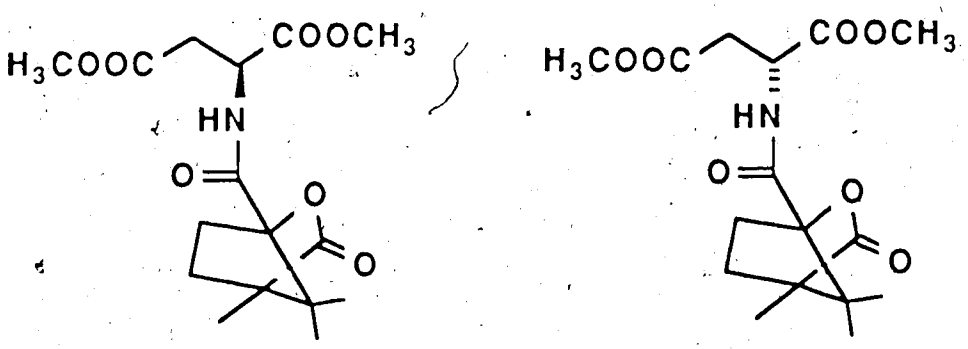
were prepared from authentic L and from racemic aspartic acid. The ^1H NMR spectrum allowed detection of about 0.5 % of one diastereomer in the presence of the other.

Scheme 31.



91
92 2R isomer

97
98 2R isomer



99

100

The camphanamide methyl esters prepared from the experimental amino acids **97** and **98** showed no trace of the "other " diastereomer. Therefore the enantiomeric purity was estimated to be ≥ 99 %.

In conclusion, a method to prepare α-hydrazino and α- oxyamino acids from α- hydroxy acids in high enantiomeric purity has been developed. Although attempts to prepare the N-hydroxy amino compound

have not been successful, the protected derivatives synthesised can, in principle, be used to prepare peptides. The enzyme inhibition studies described in the appendix indicate compounds **85**, **86**, **91** and **92** are good enzyme inhibitors. They are currently under further study for anti-microbial activity.

Experimental

General

All reactions were done under a positive pressure of dry Ar; those requiring non-aqueous conditions were performed using oven-dried glassware which was cooled under Ar. All solvents were distilled before use. The solvent described as "hexanes" was distilled skelly b. All solvent mixtures are listed as volume ratios and percentages (v/v). All organic layers obtained from extractions were dried over anhydrous Na_2SO_4 or $MgSO_4$. The term "*in vacuo*" refers to the removal of solvent on a rotary evaporator followed by evacuation (< 0.05 mm Hg) to constant sample weight. All reactions were monitored by TLC using either UV adsorption, I_2 staining, ninhydrin (amino acids) or p-dimethyl aminobenzaldehyde - HCl (hydrazino acids) for visualization. Commercial thin-layer chromatography (TLC) plates were silica, Merck 60F-254. Silica gel for column chromatography was Merck type 60, 70 - 230 mesh. Flash chromatography employed by the method of Still *et al* [239], with Merck type 60 silica gel, 230 - 420 mesh.

All literature compounds had ^1H NMR, MS and IR spectra consistent with assigned structures. Melting points were determined either on a Thomas Hoover or Buchi apparatus using open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker WP - 80, WH - 200, AM - 300, WM - 360 or WH - 400 instruments in the specified deuterated solvent with tetramethylsilane (TMS) as internal standard. All reports of ^1H NMR spectra are first order approximations.

Infrared spectra (IR) were determined with a Nicolet 7199 FT- IR spectrometer. Mass spectra (MS) were recorded with an ionizing voltage of 70 eV on an AEI MS-50 instrument for electron impact (EI) ionization and on a MS-12 for chemical ionization (CI). Optical rotations were measured on Perkin-Elmer 241 or 141 polarimeters with a microcell (100 mm, 0.9 mL) or a standard cell (100 mm, 8 mL) respectively, at ambient temperatures (22 - 24 °C).

High pressure liquid chromatography (HPLC) was done using a Hewlett Packard 1082B instrument fitted with a Whatman Partisil M9 10/25 column and UV detector set at 254 nm. All gas chromatography (GC) was performed on a Hewlett Packard 5890A gas chromatograph fitted with an Alltech 10 m x 0.53 mm bonded FSOT polyphenylmethylsiloxane (RSL-300) column with He as the carrier gas. Compounds were detected using a flame ionization detector.

(*R*)-2-Amino-3-methylbutan-1-ol (3).

A modification of the procedure of Hsuno *et al* [112] was followed. A mixture of lithium aluminium hydride (30 g, 0.79 mol) and THF (1.5 L) was heated to reflux under argon for 30 min. The mixture was cooled to 0 °C and D-valine (70 g, 0.60 mol) was added in small portions. Heating under reflux was continued for 17 h, celite (40 g) was then added, followed by water (40 mL), 10% aqueous sodium hydroxide (40 mL), and water (120 mL). The mixture was filtered and the solid was washed with ethyl acetate (2 x 200 mL). The combined filtrates were concentrated *in vacuo* and the residue was distilled under reduced pressure to give 52.1 g (84 %) of **3** as a

colourless oil: bp 56 - 58 °C at 0.5 mm Hg, lit.[240] bp 55 - 57 °C at 2 mm Hg; $[\alpha]_D$ = - 14.0 ° (neat), lit.[240] $[\alpha]_D$ = + 14.6 ° (neat) for *S* enantiomer; IR ($CHCl_3$ cast) 3288 , 2960 br, 1590, 1468, 1337, 1319, 1054 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.64 (dd, 10.4, 4.1 Hz, 1 H), 3.40 (dd, 10.4, 8.0 Hz, 1 H,), 2.57 (m, 1 H), 2.36 (br s, 3 H), 1.57 (m, 1 H), 0.95 (d, 6.8 Hz, 6 H); exact mass 104.1085 (MH^+ 104.1075 calculated for $C_5H_{14}NO$).

(*S*)-2-Amino-3-methylbutan-1-ol (4).

The procedure used to transform D-valine into **3** was employed to convert L-valine (35.0 g, 0.3 mol) to 18.3 g (60% yield) of **4** as a colourless oil: bp 51 - 53 °C at 0.5 mm Hg, lit.[240] bp 55 - 57 °C at 2 mm Hg; $[\alpha]_D$ = +14.7 ° (neat), lit.[240] $[\alpha]_D$ = +14.6 ° (neat) ; all other physical constants were identical to those of **3**.

(*R*)-4-Isopropyloxazolidin-2-one (5).[110,111]

A modification to the procedure of Newman *et al* [111] was used. Phosgene (7.0 mL, 110 mmol) was added to a stirred solution of **3** (10.0 g, 97 mmol) in toluene (300 mL) at 0 °C by distillation. Triethylamine (13.5 mL, 110 mmol) was added dropwise to the resulting white slurry and the mixture was refluxed for 20 min. The triethylamine hydrochloride formed was removed by filtration after cooling, and the filtrate was concentrated *in vacuo* to give 15.4 g of an orange liquid that crystallized on standing. The product was purified by flash chromatography [239] (hexane 60%/ethyl acetate 40%) and recrystallized from hexane/ethyl acetate to give 9.71 g (77% yield) of **5** as fine white crystals: $[\alpha]_D$ = -13.6 ° (c 7.0, CHCl3), lit.[108]

$[\alpha]_D$ = +14.8 ° (c 7.0, $CHCl_3$) for *S* isomer, mp 71 - 72 °C, lit.[108] mp 71 - 72 °C; IR ($CHCl_3$ cast) 3260 , 2960, 1746, 1248, 1092, 937, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (br s, 1 H), 4.46 (t, 8.8 Hz, 1 H), 4.13 (dd, 8.8, 7.3 Hz, 1 H,), 3.62 (m, 1 H), 1.75 (m, 1 H), 0.96 (d, 6.9 Hz, 3 H), 0.91 (d, 6.8 Hz, 3 H) exact mass 129.0790 (129.0790 calculated for $C_6H_{11}NO_2$).

(*S*)-4-Isopropyloxazolidin-2-one (6).[110, 111]

The procedure used to prepare **5** from **3** was used except in this case L-valinol **4** (S enantiomer of **3**) was transformed to the corresponding oxazolidinone **6**. The compound showed spectral characteristics identical to those of **5**. $[\alpha]_D$ = +14.4 ° (c 7.0, $CHCl_3$). lit.[110] $[\alpha]_D$ = +14.8 ° (c 7.0, $CHCl_3$)

(*R*)-3-(Phenylacetyl)-4-isopropyloxazolidin-2-one (7).

The procedure of Evans and co-workers was adapted.[110] Butyllithium (12.6 mL, 0.91 M in hexane, 0.011 mol) was added dropwise to an ice cold solution of **5** (1.49 g, 0.011 mol) in dry THF (15 mL). The solution was stirred for 15 min and a solution of phenylacetyl chloride (1.5 mL, 0.011 mol) in THF (5 mL) was added, and after 0.5 h of stirring, sat. aq. sodium bicarbonate (25 mL) was added. The mixture was extracted with ether (3 x 25 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Flash chromatography [239] (15 x 5 cm, 15 % EtOAc / hexanes) gave 1.82 g (64 %) of **7** as a colourless oil.

[α]$_D$ = - 82.9 ° (c 2.6, $CHCl_3$); IR ($CHCl_3$ cast) 2960, 1776, 1700, 1255, 1355 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.31 (br s, 5 H) , 4.60 - 4.51 (m, 5 H), 2.26-2.20 (m, 1 H), 0.91 (d, 7 Hz, 3 H), 0.82 (d, 7 Hz, 3 H); exact mass 247.1206 (247.1208 calcd for $C_{14}H_{17}NO_3$). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.10; H, 6.81; N, 5.39.

(*S*)-3-(Phenylacetyl)-4-isopropyloxazolidin-2-one (8).

The procedure used to transform **5** to **7** was repeated using **6** (0.645 g, 5.00 mmol) and phenylacetyl chloride (0.664 mL, 5.00 mmol) to give 1.10 g (89 % yield) of **8**. The compound showed spectral characteristics identical to **7**. [α]$_D$ = + 74.8 ° (c 2.8, $CHCl_3$).

(*R*)-3-(Butanoyl)-4-isopropyloxazolidin-2-one (9).[106]

The procedure used for preparation of **7** was repeated using **5** (1.29 g, 10.0 mmol) and butanoyl chloride to give 1.74 g (87 % yield) of colourless oil **9**. The material showed spectral and chromatographic properties identical to those of **10**. [α]$_D$ = - 87.7 ° (c 3.6, $CHCl_3$).

(*S*)-3-(Butanoyl)-4-isopropyloxazolidin-2-one (10).[106]

The procedure used to transform **5** to **7** was employed using **6** (0.645 g, 5.00 mmol) and butanoyl chloride. The compound was purified using flash chromatography[239] (20 % EtOAc / hexanes) to furnish 0.963 g (96 % yield) of colourless oil **10**: [α]$_D$ = + 88.9 ° (c 3.6, $CHCl_3$); IR ($CHCl_3$ cast) 2980, 1777, 1699, 1382, 1202 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) δ 4.62 - 4.15 (m, 3 H), 3.17 - 2.77 (m, 2 H), 2.00 - 1.47 (m, 2 H), 1.15 - 0.80 (m, 9 H);

exact mass 199.1206 (199.1209 calcd for $C_{10}H_{17}NO_3$). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.29; H, 8.56; N, 6.91.

Oxodiperoxomolybdenum (pyridine) (hexamethylphosphoric triamide) complex (MoOPH). [37, 38]

This reagent was prepared using the procedure of Vedejs and coworkers.[38] Molybdenum (VI) oxide (MoO_3) (30.0 g, 0.208 mol) was added to a vigorously stirred solution of 30 % aq. hydrogen peroxide (150 mL, 2.5 mol) and the mixture was stirred for 3.5 h. Hexamethylphosphoric triamide (HMPT) (37.3 g, 0.208 mol) was added and the yellow precipitate formed was filtered and recrystallised from methanol and dried over phosphrous pentoxide *in vacuo* to furnish a pale yellow precipitate of MoO_5 .HMPA (12.1 g, 16 %). This complex (11.0 g, 0.030 mol) was dissolved in THF (20 mL) and the solution was filtered. The filtrate was cooled to 0 °C and pyridine (2.50 mL, 0.030 mol) was added dropwise to give a yellow precipitate which was filtered and dried *in vacuo* (11.2 g, 83 %). IR (Nujol, mull) 1480, 1457, 1300, 1093, 992, 958, 762, 752,622, 605, 582 cm^{-1}. MS (Glycerol / Sulfolane, NegFAB) 434.

(4*R* , 2'*R*)-3-[2-((Benzoyl)oxy)-2-phenyl-1-oxoethyl]-4-isopropyloxazolidin-2-one (11) and (*R*)-3-Benzoyl-4-isopropyloxazolidin-2-one (13), Procedure a .

A solution of 7 (0.476 g, 1.93 mmol) in dry THF was added to a solution of lithium diisopropylamide (1.93 mmol) in THF (15 mL) at - 78 °C. After 0.5 h, a solution of benzoyl peroxide (0.466 g, 1.93 mmol) in THF (3 mL) was

added and the mixture was slowly warmed to 0 °C. After 2 h, acetic acid (0.17 mL) was added followed by water (30 mL) and the mixure was extracted with ether (3 x 20 mL). The ether extracts were dried (Na_2SO_4) and evaporated to give a yellowish gum. Flash chromatography [239] (25 % EtOAc / Hexanes) gave **11** (0.151 g, 21 %) and **13** (0.066 g, 14 %). Spectral data for **11** and **13** are as follows.

For **11**: $[\alpha]_D$ = - 151.8° (c 2.4, $CHCl_3$); mp 86 - 90 °C; IR ($CHCl_3$ cast) 1781, 1709, 1387, 1251, 1106 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) δ 8.22 - 7.80 (br s, 2 H), 7.85 - 7.22 (br s, 8 H), 4.50 - 4.05 (m, 4 H), 2.72 - 2.30 (m, 1 H), 1.05 (d, 7.0 Hz, 3 H), 0.90 (d, 7.0 Hz, 3 H); exact mass 367.1418 (367.1419 calcd for $C_{21}H_{21}NO_5$). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found : C, 68.55; H, 5.71; N,3.64.

For **13**: mp 139 -141 °C; IR ($CHCl_3$ cast) 1788, 1680, 1314, 1295, 1110 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.07 - 7.87 (m, 2 H), 7.72-7.17 (m, 3 H), 4.80 - 4.05 (m, 3 H), 2.70 - 2.17 (m, 1 H), 0.90 (d, 6.0 Hz, 6 H); exact mass 233.1056 (233.1052 calcd for $C_{13}H_{15}NO_3$).

Independent preparation of 13 from 5.

A solution of butyllithium (1.075 M in hexanes, 0.74 mL, 0.79 mmol) was added to a solution of **5** (0.100 g, 0.775 mmol) in dry THF (10 mL), cooled in an ice bath. After 0.5 h of stirring a solution of benzoyl chloride (0.093 mL, 0.791 mmol) in dry THF was added dropwise. The mixture was stirred for 2 h and sat. aq. sodium bicarbonate (5 mL) was added. The solution was extracted with ether (3 x 15 mL). The ether extracts were dried (Na_2SO_4) and evaporated to furnish a yellow solid. Flash chromatography

[239] (25 % EtOAc / hexanes) gave a white crystalline solid (0.124 g, 68 %). The material showed spectral and chromatographic properties identical to those of compound **13** obtained from the reaction used to transform **8** to **11**.

(4*R* , 2'*R*)-3-[2-((Benzoyl)oxy)-2-phenyl-1-oxoethyl]-4-isopropyloxazolidin-2-one (11) Procedure b .

Procedure a for oxidation of **7** to **11** was repeated except lithium hexamethyldisilazane (Li HMDS) was used as a base instead of lithium diisopropylamide (LDA), and a solution of benzoyl peroxide (0.526 g, 2.17 mmol) in THF dried over anhydrous sodium sulfate and molecular sieves was used. Carboximide **7** (0.573 g, 2.31 mmol) was transformed to give, after purification as above, 0.432 g (54 % yield) of **11** along with 0.111 g (22 %) of **13** .

(4*S* , 2'*S*)-3-[2-((Benzoyl)oxy)-2-phenyl-1-oxoethyl]-4-isopropyloxazolidin-2-one (12).

The procedure (procedure b *vide supra*) used to transform **7** to **11** was repeated using **8** (0.120 g, 0.485 mmol) to furnish 0.118 g (64 %) of **12** along with compound **14**, the *S* enantiomer of compound **13**. Compound **12** shows spectral and chromatographic properties identical to compound **11** with $[\alpha]_D = +157.2°$ (c 2.9, $CHCl_3$)

Compound **14** shows chromatographic behaviour and spectral properties identical to those of **13**.

Ethanolysis of 12 to ethyl mandelate (15).

A solution of lithium ethoxide (prepared from dry ethanol (1 mL) and butyllithium (1.16 M in hexanes, 0.5 mL, 0.580 mmol)) was added to a solution of 12 (0.216 g, 0.588 mmol) in dry THF cooled to - 78 °C. The solution was warmed to room temperature and stirred for 1.5 h. Acetic acid (0.035 mL) in THF (1 mL) was added followed by a saturated aq. solution of ammonium chloride (3 mL), and the mixture was extracted with ether (3 x 15 mL). The ether layers were dried (Na_2SO_4) and evaporated to give a yellow oil. Flash chromatography [239] (25 % EtOAc / hexanes) gave 0.092 g (88 %) of **15** as colourless oil. $[\alpha]_D$ = + 55.4° (c 6.5 acetone); lit[1,13] $[\alpha]_D$ = - 86.2° (c 4.0 acetone) for R isomer; IR ($CHCl_3$ cast) 3465, 2888, 1732, 1260, 1210, 1185, 1050; 1068, 1020, 730, 698 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.55-7.25 (br s, 5 H), 5.16 (d, 5.6 Hz, 1 H), 4.22 (q, 8.0 Hz, 2 H); 3.55 (d, 5.6 Hz, 1 H), 1.17 (t, 8.0 Hz, 3 H); exact mass 180.0787 (180.0787 calcd for $C_{10}H_{12}O_3$).

(4*S* , 2'*S*)-3-[2-((Benzoyl)oxy)-1-oxobutyl]-4-isopropyloxazolidin-2-one (16).

The procedure b (*vide supra*) used to transform 7 to 11 was repeated using **10** (0.223 g, 1.12 mmol) and benzoyl peroxide (0.271 g, 1.11 mmol) to furnish 0.116g (32 % yield) of **16** after purificaton by flash chromatography [239] (15 % EtOAc / hexanes): IR ($CHCl_3$ cast) 2960, 1779, 1711, 1680, 1389, 1209 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.16 - 7.92 (br s, 2 H), 7.74 - 7.40 (br s, 3 H), 5.32 (q, 4.0, 10.0 Hz, 1 H), 4.60 - 4.08 (m, 3 H), 2.64 - 2.36 (m, 1 H), 2.24 - 1.74 (m, 2 H), 1.10 - 0.80 (m, 9 H); exact mass 319.1410

(319.1419 calcd for $C_{17}H_{21}NO_5$); MS (CI NH_3) 337 ($M^+ \cdot NH_4$). Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.83; H, 6.77; N, 4.37. Found: C, 63.65; H, 6.87; N, 4.66.

(*R*)-*N*-Benzyloxycarbonyl valine (17).[114]

Benzyl chloroformate (3.74 g, 0.021 mol) was added over 0.5 h to a vigorously stirred solution of D-valine (2.34 g, 0.020 mmol) in 17 % aq. $NaHCO_3$ (25 mL) cooled in an ice bath. The mixture was stirred for 12 h and was extracted with ether (50 mL). The aqueous layer was acidified to pH 2 using 5.7 M HCl and was extracted with ether (3 x 50 mL). The ether layers from the second extraction were dried (Na_2SO_4) and concentrated *in vacuo* to give 2.30 g (45 % yield) of pure colourless gum **17**: IR ($CHCl_3$ cast) 3310, 2968, 1719, 1518, 1220, 1205, 1095, 1040, 698 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.80 (br s, 1 H), 7.30 - 7.20 (br s, 5 H), 5.40 - 5.20 (br s, 1 H), 5.16 (br s, 2 H), 4.48 - 4.24 (m, 1 H), 2.40 - 2.00 (m, 1 H), 1.00 (t, 6.0 Hz, 6 H); exact mass 251.1165 (251.1153 calcd for $C_{13}H_{17}NO_4$).

(*R*)-*N*-Phenyl[2-(((benzyloxy)-carbonyl)amino)-3-methyl]butanamide (18).

A solution of DCC (4.00 g , 0.019 mol) in dry THF (50 mL) was added over 10 min to a solution of *N*-CBZ D -valine **17** (5.00 g, 0.019 mol), aniline (2.00 mL, 0.021 mol), and 3-hydroxybenzotriazole (2.71 g, 0.020 mol) in dry THF (150 mL), and the mixture was stirred for 3 h.[116] Precipitated dicyclohexyl urea was removed by filteration, and ether (400 mL) was added to the filtrate which was washed with 1N HCl (120 mL). The

organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* to give 9.96 g of solid. Chromatography over silica gel 60 (2 % MeOH/$CHCl_3$) gave 3.95 g (62 % yield) of **2** ; mp 172 - 174 °C; IR ($CHCl_3$ cast) 3298, 1690, 1659, 1533, 1246 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.88 (br s, 1 H), 7.40 - 7.24 (br s, 9 H), 7.12 (br t, 1 H), 5.44 (br d, 1 H), 5.12 (s, 2 H), 4.08 (q, 5.0, 6.7 Hz, 1 H), 2.36 - 2.14 (m, 1 H), 1.00 (t, 8.0 Hz, 6 H); exact mass 326.1623, (326.1630 calcd. for $C_{19}H_{22}N_2O_3$).

(*R*)-*N*-Phenyl(2-amino-3-methyl)butanamide (19) from 18.

Compound **18** (1.80 g, 5.52 mmol) was hydrogenolysed [118] over 5 % Pd/C (0.50 g) in ethyl acetate (50 mL) and glacial acetic acid (1 mL) for 8 h under 1 atm of H_2 pressure. The catalyst was removed by filteration (celite pad), ether (50 mL) was added to the filtrate, and the mixture was washed with sat. aq. $NaHCO_3$ (3 x 20 mL). The organic layer was separated and extracted with 0.5 M HCl (3 x 15 mL). The aqueous layer was brought to pH 12 using 10 % aq. NaOH and extracted with ether (3 x 50 mL). The ether layers were dried (Na_2SO_4) and were concentrated to give 0.925 g (87 % yield) of colourless gum **19**: IR ($CHCl_3$ cast) 3300, 2958, 1664, 1600, 1522, 1442, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.52 (br s, 1 H), 7.60 and 7.32 (br s, 4 H), 7.10 (br s, 1 H), 3.39 (d, 3.5 Hz, 1 H), 2.56-2.30 (m, 1 H), 1.64 (br s, 2 H), 1.05 (d, 7.0 Hz, 3 H), 0.88 (d, 7.0 Hz, 3 H); exact mass 192.1268 (192.1262 calcd. for $C_{11}H_{16}N_2O$).

(*R*)-*N*- (2-Amino-3-methyl)butyl aniline (20) from amide 19.

A modification of the literature procedure was followed.[120] Lithium aluminium hydride (0.400 g, 10.52 mmol) was added to a solution of **19** (0.839 g, 4.36 mmol) in dry THF, and the mixture was refluxed for 3 h. The mixture was cooled to room temperature. Celite (1 g) and water (2 mL) were added followed by 10 % aq. NaOH (2 mL) and water (4 mL). The mixture was extracted with ether (50 mL). The ether layers were dried (Na_2SO_4) and concentrated to give 0.437 g (56 % yield) of colourless oil **20**: IR ($CHCl_3$ cast) 3380, 2955, 1605, 748 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.37 - 7.00 and 6.80 - 6.45 (br s, 5 H), 3.32 - 2.00 (br m, 6 H), 1.87-1.30 (m, 1 H), 0.87 (d, 4.0 Hz, 3 H), 0.80 (d, 4.0 Hz, 3 H); exact mass 178.1476 (178.1470 calcd. for $C_{11}H_{18}N_2$)

(*R*)-1-Phenyl-4-isopropylimidazolidin-2-one (21) from amine 20.

The procedure of Newman was used.[111] Phosgene (3 mL) was added to a mixture of 30 % aq. KOH (20 mL) and a solution of **20** in toluene (40 mL) at 0 °C in a flask equipped with a dry ice cold finger condenser. The mixture was stirred overnight (12 h) and was then extracted with ether (100 mL). The ether extracts were dried (Na_2SO_4) and were concentrated to give 0.470 g of semicrystalline solid. Flash chromatography (2 x 30 cm, 40 % ethyl acetate/ hexane) gave 0.440 g of **21** as a crystalline solid (87 % yield); mp 112 - 114 °C; IR ($CHCl_3$ cast) 3320, 1719, 1600, 1502, 1475, 1412, 1917, 749 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.56 and 7.32 (br s, 4 H), 7.05 (br s, 1 H), 5.20 - 4.60 (br s, 1 H), 3.94 (m, 1 H), 3.56 (m, 2 H), 1.9 - 1.5 (m, 1 H), 0.99 (d, 5.5 Hz, 3 H), 0.95 (d, 5.5 Hz, 3 H); exact mass

204.1264 (204.1262 calcd. for $C_{12}H_{16}N_2O$). Anal. calcd. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.89; N, 13.71. Found : C, 70.14; H, 7.71; N, 13.44.

Dibenzyl peroxydicarbonate (22).

A modification of the literature procedure [121] was used with precautions appropriate to dealing with organic peroxides.[121] Cold (0 °C) solutions of hydrogen peroxide (2.7 mL, 30 % in H_2O, 24 mmol) and 2.35 M NaOH (20 mL) were mixed and added with rapid stirring over 15 min to benzyl chloroformate (8.02 g, 47 mmol) at 0 °C. Hexane (30 mL) was added and the mixture stirred for 15 min and filtered. The precipitate was washed with hexane (3 x 15 mL), dissolved in $CHCl_3$, and was dried ($MgSO_4$). Slow addition of hexane gave a crystalline precipitate, which was filtered, washed with hexane (2 x 15 mL), and dried in vacuo (20 °C) to give 2.8 g (53 % yield) of dibenzyl peroxydicarbonate **22**: mp 101 °C dec (lit.[121] mp 101 - 102 °C); IR (CH_2Cl_2 cast) 1798, 1456, 1376, 1228, 1206 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) δ 7.40 (br s, 10 H), 5.32 (s, 4 H). Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.66 Found: C, 63.52; H, 4.64.

Oxidation of 7 to (4*R* , 2'*R*)-3-[2-(((Benzyloxy)carbonyl)oxy)-2-phenyl-1-oxoethyl]-4-isopropyloxazolidin-2-one (23).

A 0.044 M solution of $LiN(Me_3Si)_2$ (4.0 mL, 1.7 mmol) was added to a solution of oxazolidinone carboximide **7** (401 mg, 1.62 mmol) in THF (2 mL) at - 78 °C. The solution was stirred for 0.5 h, and a solution of dibenzyl peroxydicarbonate **22** (480 mg, 1.59 mmol) in THF (4 mL) was added. Stirring at - 78 ° was continued for 0.5 h, and acetic acid (96 mg, 1.6 mmol)

was added. The solution was warmed to 0 °C, water (20 mL) was added, and the resulting mixture was extracted with ether (3 x 20 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* , and purified by flash chromatography [239] (30 % EtOAc / hexane). Recrystallisation (EtOAc / hexanes) gave 526 mg (82 %) of **23** : mp 160 - 161 °C; [a]$_D$ = - 121.7 ° (c 3.0, $CHCl_3$); IR (CH_2Cl_2 cast) 3060, 1782, 1746, 1709, 1387, 1244 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.7-7.3 (br s, 10 H), 7.27 (s, 1 H), 5.16 (s, 2 H), 4.4-4.0 (m, 3 H), 2.6-2.2 (m, 1 H), 0.95 (d, 6.0 Hz, 3 H), 0.85 (d, 6.0 Hz, 3 H); exact mass 397.1525 (397.1526 calcd for $C_{22}H_{23}NO_6$). Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.48; H,5.83; N, 3.41. Found: C, 66.50; H, 5.83; N, 3.56.

Oxidation of 8 to (4*S* , 2'*S*)-3-[2-(((Benzyloxy)carbonyl)oxy)-2-phenyl-1-oxoethyl]-4-isopropyloxazolidin-2-one (24).

The procedure used to transform **7** to **23** was employed. Carboximide **8** (0.247 g, 1.00 mmol) was transformed using **22** (0.310, 1.02 mmol) to give 0.245 g (61 % yield) of **24**. The material showed spectral and chromatographic characteristics similar to those of **23**. For **24**: mp 157 - 158 °C;

[a]$_D$ = + 110.5 ° (c 4.9, $CHCl_3$).

(4*R* , 2'*R*)-3-[2-(((Benzyloxy)carbonyl)oxy)-1-oxobutyl]-4-isopropyloxazolidin-2-one (25).

The procedure used to transform **7** to **23** was employed to oxidise **9** (1.54 g, 7.73 mmol) using **22** ([illegible] g, 7.78 mmol) to give 2.42 g (89 % yield)

of **25**. The chromatographic behaviour and spectral data are identical to those of **26**. For **25**: $[\alpha]_D$ = - 14.2 ° (c 2.6, $CHCl_3$).

(4*S*, 2'*S*)-3-[2-(((Benzyloxy)carbonyl)oxy)-1-oxobutyl]-4-isopropyloxazolidin-2-one (26).

The procedure for enolisation and oxidation used to transform **7** to **23** was employed using carboximide **10** (0.202 g,1.01 mmol) to furnish 0.308 g (87 % yield) of **26** : mp 96 - 97 °C; $[\alpha]_D$ = + 13.8 ° (c 2.6, $CHCl_3$); IR ($CHCl_3$ cast) 2880, 1781, 1748, 1713, 1389, 1280, 1247, 1205 cm^{-1}; 1H NMR (360 MHz, $CDCl_3$) δ 7.40 - 7.30 (br s, 5 H), 5.85 (dd, 3.2, 8.4 Hz, 1 H), 5.18 (br s, 2 H), 4.5 - 4.2 (m, 3 H), 2.5 - 2.3 (m, 1 H), 2.0 - 1.7 (m, 2 H), 1.04 (t, 7.0 Hz, 3 H), 1.0 - 0.80 (m, 6 H); exact mass 349.1525 (349.1525 calcd for $C_{18}H_{23}NO_6$). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.63; N 4.00. Found: C, 61.49; H, 6.61; N, 4.16.

Hydrolysis of 23 to (*R*)-(-)-mandelic acid (27).

Solid potassium hydroxide (170 mg, 3.04 mmol) was added to a solution of **23** (obtained from oxidation of **7**) (238 mg, 0.609 mmol) in water / THF (1:3, 4 mL). The mixture was stirred at 20 °C for 4 h, extracted with ether (3 x 15 mL), acidified to pH 2 with 5.7 M HCl, and extracted with ether (3 x 15 mL). The organic phases from the second extraction were dried ($MgSO_4$) and concentrated *in vacuo* . The resulting crude mandelic acid was converted to its potassium salt by using aq. $KHCO_3$, and this was purified by ion-exchange on Bio-rad AG1 (acetate form) with water and 2.5 N CF_3COOH as eluent. Concentration *in vacuo* gave (*R*)-(-)-mandelic

acid: mp 129 - 130 °C (lit.[122] mp 131 - 133 °C); $[\alpha]_D$ = - 128.5 ° (c 2.5, H_2O) (lit.[122] $[\alpha]_D$ = -153.0 ° (c 2.5, H_2O).

Independent preparation and separation of 23 and its 2'*S* diastereomer 28.

Butyllithium (0.091 M in hexanes, 24.1 mL, 20.0 mmol) was added to a solution of (±)- mandelic acid (1.52 g, 10.0 mmol) in THF (5 mL) at - 78 °C. A solution of benzyl chloroformate (2.85 mL, 20.0 mmol) in THF was added, the mixture was extracted with ether (3 x 25 mL) to rempve impurities, and the aqueous phase was acidified to pH 2 with HCl before extraction of the product with ether (3 x 25 mL). These ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 2.51 g (87 % yield) of 2-[((benzyloxy)carbonyl)oxy]-2-phenylacetic acid **29** : mp 117 - 119 °C (lit.[123] mp 123 - 125 °C); IR ($CHCl_3$ cast) 3450, 3000, 1727, 1247 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) δ 9.97 (br s, 1 H), 7.32 (br s, 10 H), 5.87 (s, 1 H), 5.17 (s, 2 H); MS (CI NH_3) 304 ($M^+ \cdot NH_4$). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92. Found: C, 67.24; H, 5.04.

A solution of **29** in benzene (5 mL) at 5 °C was treated with oxalyl chloride (0.20 mL, 2.4 mmol) and stirred for 12 h. The volatile components were removed *in vacuo* (5 mm of Hg) and the residue was dissolved in dry THF (2 mL). This solution was added to a cooled (0 °C) solution of the anion generated from **5** (123 mg, 1.0 mmol) and butyllithium (0.91 M in hexanes, 1.20 mL, 1.09 mmol) in THF (5 mL).[106] The mixture was stirred for 30 min, 5 % sodium bicarbonate solution (4 mL) was added, and the product was extracted with ether (3 x 15 mL). The organic phase was dried

(Na_2SO_4), concentrated *in vacuo* , and purified by flash chromatography [239] (30 % EtOAc / hexane) to give 154 mg (38 %) of a mixture of **23** and its 2' *S* diastereomer **28**. Although the two compounds showed similar spectral and thin-layer chromatographic behavior, the 2'*S* isomer could be clearly distinguished by ^{1}H NMR by its 2' proton resonance at δ 7.08 (s, 1 H) and by its isopropyl methyl resonances at δ 0.76 (d, 6 Hz, 3 H) and 0.43 (d, 6 Hz, 3 H).

Separation of the two isomers was achieved by HPLC on a silica gel column (Whatman Partisil 10 M9/25) using a 35 - 40 % gradient of EtOAc / hexanes at 20 °C with a flow of 2 mL / min. The retention times of **23** and its 2'*S* isomer **28** were 9.30 min and 10.33 min, respectively. Injections of **23** obtained by oxidation of **7** with **22** gave the peak at 9.3 min but showed no detectable peak at 10.3 min.

3-Phenylpropanoyl chloride from 3-phenylpropanoic acid.

Thionyl chloride (3.03 g, 0.025 mol) was added to a solution of 3-phenylpropanoic acid (3.01 g, .020 mol) in THF (25 mL) and the mixture was refluxed for 0.5 h . The volatile components were removed under reduced pressure using a water aspirator and the residual yellow oil was distilled to give a colourless oil (2.31 g, 68 %). bp 111 - 112 °C at 14 mm of Hg. (lit. [241] 109 °C at 11 mm of Hg); IR 3030, 1804, 1792, 1497, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (br s, 5 H), 3.25 (t, 7.2 Hz, 2 H), 3.00 (t, 7.2 Hz, 2 H); exact mass 168.0341 (168.0341 calcd for C_9H_9ClO).

(*S*)-3-[(3-Phenyl)propanoyl]-4-isopropyloxazolidin-2-one (31).[91]

The procedure used for preparation of **7** was repeated using **6** (0.650 g, 5.03 mmol) and 3-phenylpropanoyl chloride. The compound was obtained as a white crystalline solid (0.870 g, 66 % yield). mp 59 - 60 °C $[\alpha]_D$ = + 62.7 ° (c 2.0, $CHCl_3$); IR ($CHCl_3$ cast) 2955, 1796, 1773, 1706, 1392, 1363, 1211,701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.10 (br s, 5 H), 4.16-4.04 (m, 2 H), 4.38-4.28 (m, 1 H), 3.34-3.22 (m, 1 H), 3.22- 3.08 (m, 1 H), 3.02-2.88 (m, 2 H), 2.34-2.22 (m, 1 H), 0.82 (d, 7.0 Hz, 3 H), 0.78 (d, 7.0 Hz, 3 H); exact mass 261.1369 (261.1365 calcd for $C_{15}H_{19}NO_3$). Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.35. Found: C, 69.00; H, 7.35; N, 5.22.

(*R*)-3-(3-Methylbutanoyl)-4-isopropyloxazolidin-2-one (32). [91]

The procedure used for preparation of **7** was repeated using **5** (0.610 g, 4.72 mmol) and isovaleryl chloride. Compound **32** was obtained in 98 % yield (0.987 g) as a colourless oil after purification by flash chromatography [239] (15 % EtOAc / Hexanes): [a]$_D$ = - 75.5 ° (c 4.8; $CHCl_3$); IR ($CHCl_3$ cast) 2962, 1782,1701, 1388, 1374, 1305, 1206 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 4.62 - 4.12 (m, 3 H), 3.17 - 2.62 (m, 2 H), 2.61 - 1.95 (m, 2 H), 1.12 - 0.82 (m, 12 H); exact mass 213.1365 (213.1364 calcd for $C_{11}H_{19}NO_3$). Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.97; N, 6.56. Found: C, 61.87;, H, 9.04; N, 6.51.

(*R*)-3-(2-Butenoyl)-4-isopropyloxazolidin-2-one (33).

The procedure used for preparation of **7** was repeated using **5** (1.29 g, 10.0 mmol) and 2-butenoyl chloride. The compound was obtained (1.62 g, 82 % yield) as a white crystalline solid following purification by flash chromatography [239]. mp 52 - 54 °C; [a]$_D$ = - 99.4 ° (c 5.1, $CHCl_3$); IR ($CHCl_3$ cast) 2905, 1773, 1686, 1638, 1388, 1365, 1339, 1299, 1234, 1205, 1118, 1062, 1036, 9075, 715 cm $^{-1}$; ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.47-7.00 (m, 2 H), 4.62-4.12 (m, 3 H), 2.62-2.12 (m, 1 H), 2.05-1.85 (br d, 4 Hz, 3 H), 0.95 (d, 4 Hz, 3 H), 0.85 (d, 4 Hz, 3 H); exact mass 197.1050 (197.1051 calcd for $C_{10}H_{15}NO_3$).

(4*S* , 2'*S*)-3-[2-(((Benzyloxy)carbonyl)oxy)-3-phenyl-1-oxopropyl]-4-isopropyloxazolidin-2-one (34).

The enolisation and oxidation was performed using the procedure employed to convert compound **7** to **23**. Carboximide **31** (0.261 g, 1.00 mmol) was converted using **22** (0.303 g, 1.00 mmol), to furnish 0.347 g (81 % yield) after purification by flash chromatography [239] (25 % EtOAc/hexanes). In this case 6 % of the diastereomer with the 2' *R* configuration could be detected by NMR.

34: mp 89 - 90 °C; [α]$_D$ = + 43.6 ° (c 2.5, $CHCl_3$); IR ($CHCl_3$ cast) 2960, 1779, 1747, 1712, 1388, 1245, 1205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 - 7.2 (br s, 10 H), 6.16 (dd, 3.5, 10.0 Hz, 1 H), 5.10 (m, 2 H), 4.36 (m, 1 H), 4.3 - 4.2 (m, 2 H), 3.18 (dd, 10.0, 14.0 Hz, 1 H), 2.42 (m, 2 H), 0.89 (d, 5.0 Hz, 3 H), 0.82 (m, 3 H); MS (CI, NH_3), *m/e* (relative intensity) 429 (100, M^+. NH_3). Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.19; H, 6.29; N, 3.55.

(4*R* , 2'*R*)-3-[2-(((Benzyloxy)carbonyl)oxy)-3-methyl-1-oxobutyl]-4-isopropyloxazolidin-2-one (35).

The procedure used for enolisation and oxidation to convert compound **7** to **23** was performed using carboximide **32** (0.216 g, 1.01 mmol) and **22** (0.310 g, 1.02 mmol). Compound **35** was obtained as a white, crystalline solid (0.169 g, 46 % yield) after two recrystallisations from ethyl acetate / hexanes: mp 140 - 142 °C; IR ($CHCl_3$ cast) 1768, 1745, 1716, 1402, 1390, 1297, 1263, 1248, 1234, 1208 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.38 (s, 5 H), 5.92 (d, 4.0 Hz, 1 H), 5.18 (s, 2 H), 4.62 - 4.25 (m, 3 H), 2.87 - 2.01 (m, 2 H), 1.37 - 0.85 (m, 12 H); exact mass 363.1678 (363.1682 calcd for $C_{19}H_{25}NO_6$). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.88; H, 6.86; N, 3.92.

1-[((Benzyloxy)carbonyl)oxy]-1,2-diphenylethanone (36) from 1,2-diphenylethanone.

The enolisation and oxidation was performed using the procedure used to convert **7** to **23** except KHMDS was used as a base. The material could also be obtained by use of LiHMDS or *tert* -butyllithium as a base instead of KHMDS, in 8 % and 27 % yield respectively. However, the use of KHMDS (3.20 mL, 0.31 M in THF, 0.99 mmol) (prepared by reaction of potassium hydride with hexamethyldisilazane in THF at room temperature) as a base and 1,2-diphenylethanone (0.196 g, 1.0 mmol), followed by purification by flash chromatography [239] (1% $CHCl_3$, 18 % EtOAc, hexane) gave 0.246 g (71 % yield) of pure **36**: mp 108 - 109 °C; IR ($CHCl_3$

cast) 1745, 1696, 1276, 1244, 948 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.15 - 7.92 (br s, 2 H), 7.27 - 7.17 (br s, 8 H), 6.82 (s, 2 H); MS (NH_3 CI) 364 ($M^+ \cdot NH_4$). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.06; H, 5.28. Found: C, 76.28; H, 5.23.

Ethyl 2-benzoyl-2-[((benzyloxy)carbonyl)oxy]acetate (37).

Ethyl benzoylacetate (190 mg , 1.00 mmol) was oxidised with **22** (312 mg, 1.03 mmol) by using the procedure described for conversion of **7** to **23** excepting the workup. The mixture was not quenched with acetic acid at -78 °C but instead was warmed over the course of 1 h to 0 °C. Concentrated NH_4Cl (20 mL) was added, and the mixture was extracted with ether (3 x15 mL). The dried ether extracts were concentrated *in vacuo* and purified by flash chromatography [239] (14 % EtOAc / hexane) to give 26 mg (13 %) of recovered ethyl benzoylacetate and 154 mg (45 % yield) of **37**: IR ($CHCl_3$ cast) 1751, 1695, 1278, 1234 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 8.20- 8.00 (br s, 2 H), 7.80 - 7.20 (br s, 8 H), 6.20 (s, 2 H), 4.27 (q, 7.3 Hz, 2 H), 1.20 (t, 7.3 Hz, 3 H); exact mass 342.1101 (342.1104 calcd for $C_{19}H_{18}O_6$). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H,5.29. Found : C, 66.56; H, 5.40.

1-Phenyl-2-[((benzyloxy)carbonyl)oxy]pentan-1-one (38) from valerophenone.

The procedure used for preparation of **37** was employed using KHMDS as a base. Valerophenone (163 mg, 1.0 mmol) was oxidised using **22** (0.446g, 1.47 mmol) to furnish 0.145 g (46 % yield) of **38**: IR ($CHCl_3$ cast) 1760, 1670, 1226, 695 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.4 (br s, 10

H), 5.82 (t, 7.5 Hz, 1 H), 5.25 (s, 2 H), 2.37 - 2.05 (br q, 2 H), 1.50 (m, 2 H), 0.92 (br t, 3 H); MS (CI NH_3) 330 ($M^+ \cdot NH_4$). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found : C, 73.20; H, 6.61.

Ethyl 2-phenyl-2-[((benzyloxy)carbonyl)oxy]acetate (39).

A solution of ethyl phenylacetate (0.164 g, 1.00 mmol) in THF (3 mL) was added to a solution KHMDS, prepared from potassium hydride and hexamethyldisilazane (0.338 M, 3.50 mL, 1.18 mmol) in THF, cooled to -78 °C. The mixture was stirred for 20 min and a solution of dibenzyl peroxydicarbonate 22 (0.451 g, 1.49 mmol) in THF (5 mL) was added. The mixture was stirred for 45 min and poured into sat. aq. NH_4Cl solution (20 mL), and the resulting mixture was extracted with ether (3 x 15 mL). The ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. Flash chromatography (10 % EtOAc, 10 % CH_2Cl_2, hexanes) gave (0.092 g, 29 %) of oil **39**: IR (CH_2Cl_2 cast) 1745, 1280, 1249, 1210, 1178, 1027 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) δ 7.62 - 7.25 (br s, 10 H) 5.70 (s, 1 H), 5.23 (s, 2 H), 4.16 (q, 7.3 Hz, 2 H), 1.14 (t, 7.3 Hz, 3 H); exact mass 314.1157 (314.1154 calcd for $C_{18}H_{18}O_5$); MS (CI, NH_3) 332 ($M^+ \cdot NH_4$). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.79; H, 5.79.

Benzyl carbamate (40) from reaction of ammonia with 22.

Concentrated (28 %) aq. ammonia (1 mL) was added to a solution of 22 (0.303 g, 1.00 mmol) in THF (1 mL) and the mixture was stirred for 15 min. The mixture was extracted with ether (2 x 5 mL) and chloroform (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated

in vacuo to [redacted] white solid. Recrystallisation of the white solid (EtOAc / Hexane) gave [redacted]53 g (91 % yield) of **40** : mp 88 - 89 °C (lit.[242] 87 -89 °C); IR ($CHCl_3$ cast) 3398, 3332, 3271, 3179, 1689, 1445, 1400, 1340, 1070, 731 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 (br s, 5 H), 5.12 (s, 2 H), 7.74 (br s, 2 H); exact mass 151.0628 (151.0633 calcd for $C_8H_9NO_2$); MS (CI NH_3) 169 (100 % $M^+ \cdot NH_4$).

1-Trimethylsilyloxy-1,2-diphenylethene (41) from 1,2-diphenylethanone.[124]

The procedure of House [125] and co-workers employed in preparation of **43** was used, except Li HMDS was used as a base in this preparation. 1,2-diphenylethanone (5.00 g, 0.0255 mol) was transformed using TMSCl (6.34 g, 0.058 mol). The silyl enol ether **41** could be obtained as a colourless oil (5.192 g, 76 % yield) after fractional distillation: bp 108 - 109 °C at 0.15 mm of Hg (lit.[124] bp 135 ° at 1.3 mm of Hg); IR (film) 2958, 1630, 1252. 1232, 848 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.75 -6.87 (m, 10 H), 6.12 (s) and 6.11 (s, 1 H); 0.2 (s) and 0.03 (s, 9 H); exact mass 268.1280 (268.1283 calcd for $C_{17}H_{20}OSi$).

1-Trimethylsilyloxy-1-phenylpent-1-ene (42) from Valerophenone.

The procedure of House [125] and co-workers employed in preparation of **43** was used, except lithium bis(trimethylsilyl)amide (Li HMDS) was used as a base in this preparation. Valerophenone (1.63 g, 10.0 mmol) was transformed using TMSCl (2.16 g, 20.0 mmol). Compound **42** could be

isolated as a colourless oil after distillation (1.95 g, 83 % yield): bp 109 -110 °C at 2 mm of Hg; IR (CH_2Cl_2 cast) 2959, 1252, 1075, 868, 845, 756, 696 cm^{-1}; ^1H (80 MHz, $CDCl_3$) δ 7.65 - 7.25 (m, 5 H), 5.30 (t, 7.0 Hz, 1 H), 2.21 (br q, 2 H), 1.47 (m, 2 H), 0.95 (br t, 3 H), 0.10 (s, 9 H); exact mass 234.1435 (234.1440 calcd for $C_{14}H_{22}OSi$).

2-Trimethylsilyloxy-3,3-dimethylbut-1-ene (43) from *tert*-butyl methyl ketone [125]

The compound was prepared using the procedure of House and co-workers [125]. *tert*-Butyl methyl ketone (5.00 g, 0.050 mol) in THF (8 mL) was added to a solution of lithium diisopropylamide (1.06 M in 1: 4 Hexane / THF, 47.5 mL, 50.3 mmol) cooled to - 78 °C. After a 0.5 h stirring period, trimethylchlorosilane (TMSCl) (10.8 g, 10.0 mmol) was added and the mixture was warmed to room temperature. It was stirred for 1 h and poured into sat. aq. sodium bicarbonate solution (25 mL). The mixture was extracted with ether and the ether layer was washed with water (3 x 25 mL). The ether layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellowish oil. Fractional distillation gave a colourless oil (5.13 g, 59 %) : bp 100 - 105 °C at 704 mm of Hg (lit[125] 140 - 142 ° at 760 mm of Hg.); IR (film) 2944, 1624, 1253, 1185, 847 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 4.1 (br s, 1 H), 3.95 (br s, 1 H), 1.03 (s, 9 H), 0.20 (s, 9 H); exact mass 172.1284 (172.1283 calcd for $C_9H_{20}OSi$).

1-[((Benzyloxy)carbonyl)oxy]-1,2-diphenylethanone (36) from silyl enol ether 41.

The silyl enol ether **41** (268 mg, 1.00 mmol) in THF (5 mL) was treated at 0 °C with butyllithium (0.63 mL, 1.58 M in hexane, 1.00 mmol) and stirred for 1.5 h. The solution was cooled to -78 °C , and a solution of **22** (304 mg, 1.00 mmol) in THF (3 mL) was added. The mixture was stirred at -78 °C for 15 min and warmed to - 40 °C for 1h before being poured into concentrated aq. NH_4Cl solution. The mixture was extracted with ether (3 x 20 mL), and the extracts were dried and then concentrated *in vacuo*. Flash chromatography [239] (1 % $CHCl_3$, 18 % EtOAc, hexane) of the residue gave 228 mg (66 % yield) of **36**. The chromatographic and spectral properties were identical to those of compound **36** prepared previously (*vide supra*).

1-[((Benzyloxy)carbonyl)oxy]-3,3-dimethyl-2-butanone (44) from 43.

The silyl enol ether **43** (172 mg, 1.00 mmol) was oxidised with **22** (0.302 g, 1.00 mmol) by using the procedure described for conversion of **41** to **36**. Flash chromatography [239] of the product (1 % $CHCl_3$, 18 % EtOAc, hexane) gave 155 mg (62 % yield) of a white solid **44**: mp 58 - 59 °C; IR ($CHCl_3$ cast) 2990, 1762, 1731, 1285, 1273 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.30 (br s, 5 H), 5.20 (s, 2 H), 4.92 (s, 2 H), 1.15 (s, 9 H); exact mass 250.1214 (250 1205 calcd for $C_{14}H_{18}O_4$). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24. Found: C, 67.17; H, 7.24.

Benzoin 45 from silyl enol ether 41.

Titanium tetrachloride (0.14 mL; 1.0 mmol), was added to a solution of the silyl enol ether **41** (268 mg, 1.00 mmol) in dry CH_2Cl_2 (2 mL) at - 78 °C. The mixture was stirred for 15 min, a solution of **22** (303 mg, 1.00 mmol) in THF (3 mL) was added, and the reaction mixture warmed to 20 °C for 0.5 h before being poured into ice-water (15 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography [239] (20 % EtOAc / hexane) gave 70.0 mg (33 % yield) of benzoin identical in all respects with authentic material. The stannic (tin IV) chloride reaction, which gave 19 % yield, was done similarly except that the temperature was kept at 5 °C throughout. For **45** : mp 132 - 133 °C (lit [243] 134 - 136 °C); IR (CH_2Cl_2 cast) 3415, 1678, 1449, 1205 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.07 - 7.87 (br s, 2 H), 7.62 - 7.17 (br s, 8 H), 5.98 (d, 6.0 Hz, 1H), 4.56 (d, 6.0 Hz, 1 H); exact mass 212.0837 (212.0837 calcd for $C_{14}H_{12}O_2$).

1-Phenyl-2-[((benzyloxy)carbonyl)oxy]pentan-1-one (38) from silyl enol ether 42.

The procedure used for conversion of **41** to **36** was employed using **42** (234 mg, 1.00 mmol) and **22** (0.303g, 1.00 mmol) . Flash chromatography[239] (15 % EtOAc / hexane) gave 0.113 g (36 % yield) of **38** as a colourless oil. The spectral and chromatographic properties were identical to those of **38** prepared from valerophenone.

***N*-Benzyloxyphthalimide (50)** [216]

The procedure of Chimiak [216] was adapted: Benzyl bromide (5.94 mL, 0.050 mol) was added to a mixture of *N*-hydroxyphthalimide (8.15 g, 0.050 mol) and anhydrous potassium carbonate (6.91 g, 0.050 mol) in dry DMF (50 mL), and the mixture was stirred vigorously for 48 h. The reaction mixture was poured in water (50 mL), and the solid that separated was collected by filteration and washed with water (3 x 20 mL), and was redissolved in ether (50 mL). The etheral solution was dried ($MgSO_4$) and concentrated *in vacuo* , and the residue was recrystallised from chloroform / hexanes to give **50** (9.39 g, 74 % yield): mp 145 - 146 °C (lit [216] mp 145 - 146 °C); IR ($CHCl_3$ cast) 1738, 1475, 1390, 698 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.92 - 7.25 (br s, 9 H), 5.22 (s, 2 H); exact mass 253.0747 (253.0739 calcd for $C_{15}H_{11}NO_3$).

O-Benzylhydroxylamine (51).[216]

Hydrazine (99 - 100 %, 0.475 g, 9.50 mmol) was added to a suspension of **50** (1.20 g, 4.74 mmol) in 2 % ethanol / water (51 mL) and the mixture was refluxed for 1 h, poured into 3 % aq. sodium carbonate (50 mL), and extracted with ether (3 x 20 mL). The ether extracts were washed with 3 % sodium carbonate (3 x 20 mL) dried ($MgSO_4$) and were concentrated at ≥ 10 mm pressure to give **51** as a colourless oil (0.508, 87 % yield): IR (CH_2Cl_2 cast) 1592, 1495, 1453, 1370, 1207, 1187, 995, 745, 698 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.30 (br s, 5 H), 5.12 (br s, 2 H), 4.65 (s, 2 H); MS (CI NH_3) 124 (100 % MH^+).

(4*R* , 2'*R*)-3-((2Hydroxy)-1-oxobutyl)-4-Isopropyloxazolidin-2-one (52).

A solution of **25** (1.006 g, 2.88 mmol) in ethyl acetate (25 mL) was hydrogenolysed [232] in the presence of 5% Pd/C (0.100 g) for 4 h under slightly greater (~ 5 to 10 mm of Hg) than atmospheric hydrogen pressure. The mixture was filtered through a celite 545 pad and the filtrate was concentrated *in vacuo* to give a colourless oil **52** which required no further purification (0.604 g, 97 % yield) :
$[\alpha]_D$ = - 80.6 ° (c 4.0 ,$CHCl_3$); IR (CH_2Cl_2 cast) 3502, 2967, 2938, 2878, 1782, 1697, 1487, 1464, 1388, 1365, 1308, 1245, 1205, 1122, 1058, 1018, 985, 968 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.94 (br s, 1 H), 4.46 - 4.20 (m, 3 H), 3.52 (br d, 1 H), 2.50 - 2.40 (m, 1H), 1.92 - 1.80 (m, 1 H), 1.68 - 1.52 (m, 1 H), 1.02 (t, 7.2 Hz, 3 H), 0.93 (d, 7.0 Hz, 3 H), 0.88 (d, 7.0 Hz, 3 H); exact mass 215.1159 (215.1158 calcd for $C_{10}H_{17}NO_4$); MS (CI NH_3) 233 ($M^{+\bullet}$ NH_4). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.50. Found : C, 55.70; H, 8.01; N, 6.26.

(4*R* , 2'*R*)-3-[2-((Trifluoromethanesulfonyl)oxy)-1-oxobutyl]-4-isopropyloxazolidin-2-one (53).

A solution of trifluoromethanesulfonic anhydride (0.140 mL, 0.810 mmol) in dry dichloromethane (5 mL) was added to a solution of **52** (0.174 g, 0.810 mmol) and pyridine (0.065 mL, 0.810 mmol) in dry dichloromethane (5 mL) cooled to 0 °C. The mixture was stirred for 2 h at room temperature and the solvent was evaporated using a rotary evaporator. Ether (15 mL) was added to the residue and the mixture was filtered. The filtrate was

concentrated *in vacuo* to furnish **53** as an oil (0.209 g, 74 % yield) which rapidly darkened: IR ($CHCl_3$ cast) 2975, 1814, 1784, 1744, 1415, 1274, 1209, 1145, 949 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.14 (dd, 3.2, 8.0, 1 H), 4.50 - 4.28 (m, 3 H), 2.60 - 2.40 (m, 1 H), 2.14 - 1.80 (m, 2 H), 1.13 (t, 7.2 Hz, 3 H), 0.94 (d, 7.0 Hz, 3 H), 0.90 (d, 7.0 Hz, 3 H); exact mass 347.0659 (347.0650 calcd for $C_{11}H_{16}F_3NO_6S$). Anal. Calcd for $C_{11}H_{16}F_3NO_6S$: C, 38.04; H, 4.64; N, 4.03. Found : C, 38.03; H, 4.79; N, 4.30.

(4*R* , 2'*S*)-3-[2-((Benzyloxy)amino)-1-oxobutyl]-4-isopropyloxazolidin-2-one (54).

A solution of *O*-benzyl hydroxylamine (**51**) (0.144 g, 1.17 mmol) in dry dichloromethane (4 mL) was added to a solution of freshly prepared triflate **53** (0.204 g, 0.58 mmol) in dichloromethane (4 mL) cooled in an ice bath. The mixture was stirred at room temperature for 16 h, poured into water (20 mL), and extracted with ether (3 x 15 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give 0.221 g of an oil. Flash chromatography [239] (30 % EtOAc / hexanes) gave 0.106 g (56 %) yield of colourless oil **54** : IR ($CHCl_3$ cast) 2980, 2938, 1777, 1737, 1697, 1387, 1373, 1206, 1099, 1056, 1017, 970, 751, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (br s, 5 H), 6.32 (br d, 6.0 Hz, 1 H), 4.84 (br s, 1 H), 4.68 (s, 2 H), 4.54 - 4.46 (m, 1 H), 4.30 (t, 8.8 Hz, 1 H), 4.22 (dd, 3.2, 8.8 Hz, 1 H), 2.40 - 2.30 (m, 1 H), 1.74 - 1.64 (m, 1 H), 1.50 - 1.34 (m, 1 H), 1.00 (t, 7.3 Hz, 3 H), 0.93 (d, 7.2 Hz, 3 H), 0.88 (d, 7.2 Hz, 3 H); exact mass 320.1733 (320.1730 calcd for $C_{17}H_{24}N_2O_4$); MS (CI NH_3) 321 (MH^+, 100 %). Anal.

Calcd. for C_1-$H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found : C, 63.69; H, 7.67; N, 8.39.

(*S*)-2-((Benzyloxy)amino)butyric acid, benzyl ester (55).[244]

A solution of **54** (0.100 g, 0.315 mmol) in THF (4 mL) was added to a solution of lithium benzyloxide (prepared from butyllithium (1.44 M in hexane, 0.450 mL, 0.648 mmol) and benzyl alcohol (0.073 g, 0.675 mmol)) in THF (4 mL) at 0 °C. The mixture was stirred for 0.5 h, poured into pH 7.0 phosphate buffer (5 mL) and extracted with ether (3 x 15 mL). The ether layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was purified by flash chromatography [239] (18 % EtOAc / Hexane) to give 0.041 g (44 % yield) of a colourless oil **55** [244] : IR ($CHCl_3$ cast) 1737, 1451, 1182, 1160, 970, 740, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 - 7.20 (br s, 10 H), 6.15 - 5.65 (br s, 1 H), 5.12 (s, 2 H), 4.62 (s, 2 H), 3.50 (t, 7.0 Hz, 1 H), 1.60 - 1.46 (m, 2 H), 0.82 (t, 7.7 Hz, 3 H); exact mass 299.1523 (299.1521 calcd for $C_{18}H_{21}NO_3$)

α-Aminobutyric acid (56).

A solution of **55** (0.029 g, 0.096 mmol) in 2:1 Acetic acid/ water (4 mL) was hydrogenated [232] over 5 % Pd/C (4 mg) under slight positive hydrogen pressure for 22 h. The mixture was filtered through a celite 545 pad and the filtrate was lyophilised to give a white solid (0 .0096 g, 96 % yield) of **56** : IR (KBr, pellet) 3420, 3000, 1585, 1138, 1110 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 3.71 (t, 5.8 Hz, 1 H), 1.95 - 1.75 (m, 2 H), 0.93 (t, 7.6 Hz, 3 H), MS (Glycerol / HCl pos FAB) 104 (MH^+).

Camphanamide of methyl 2-aminobutanoate 57 [220, 221] **from 56.**

A solution of (1*S* 4-)-(-)-camphanic acid chloride (0.042 g, 0.193 mmol) in toluene (C 5mL) was added to a solution of **56** (0.010 g, 0.097 mmol) in pH 10 sodium carbonate / bicarbonate buffer and the mixture was stirred vigorously for 2 h. The mixture was extracted with chloroform (2 x 5 mL) and the aqueous layer was acidified to pH 2 with 5.7 M HCl and then extracted with dichloromethane (3 x 5 mL). The organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to furnish a white solid which was dissolved in ether (2 mL). Diazomethane in ether was added until a yellow colour persisted. The mixture was evaporated *in vacuo* and the residue was analysed by GC. The coinjections with standard [220, 221] samples of camphanamide methyl esters of DL α-aminobutyric acid and L-aminobutyric acid showed that the predominant component of the parent amino acid mixture was the *S* enantiomer. Injection of the mixture obtained above without standard (160 °/ 1 min, 1.5 °/ min to 200 °, 6.6 psi He at 160 °) showed peaks at R_t = 18.94 min (camphanamide from *R* isomer) and R_t = 20.00 min (camphanamide from *S* isomer). The relative peak areas indicated that the amino acid **56** used for preparation of camphanamide methyl esters had 91.2 ± 0.2% of the *S* and 8.9 ± 0.2 % of *R* enantiomer. Pure sample of **57** was obtained by removal of the side product, methyl camphanoate, by sublimation (65 °, 0.01 mm of Hg, ~ 6 h).

For **57** : IR ($CHCl_3$ cast) 3365, 2964, 1793, 1744, 1677, 1528 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.93 (br d, 1 H), 4.62 (m, 1 H), 3.78 (s, 3 H), 2.60 - 2.88 (m, 1 H), 2.16 - 1.84 (m, 3 H), 1.83 - 1.64 (m, 2 H), 1.14 (s, 6 H), 0.98

(s, 3 H), 0.92 (m, 3 H); exact mass 297.1576 (297.1576 calcd for $C_{15}H_{23}NO_5$).

Dimethyl (*S*)-malate (59).[239]

A solution of diazomethane in ether was added to a solution of (*S*) malic acid (1.34 g, 10.0 mmol) in 50 % methanol / chloroform until the yellow color persisted. The mixture was concentrated *in vacuo* , redissolved in chloroform, and filtered through a short silica column. The filtrate was evaporated *in vacuo* to furnish 1.62 g of a colourless oil (quantitative yield) **59**: IR (CH_2Cl_2 cast) 2956, 1740, 1438, 1275, 1220, 1170, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 (q, 4.0, 6.4 Hz, 1 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 2.98 - 2.78 (m, 2 H); exact mass 163.0599 (MH^+), (163.0606 calcd for $C_6H_{11}O_5$); MS (CI NH_3) 180 (100 % $M^+ \cdot NH_4$).

Dimethyl (*R*)-malate (58).[239]

The procedure used for preparation of **59** was repeated using (*R*) malic acid (1.34 g, 10.0 mmol) to give 1.62 g (quantitative yield) of **58**. The compound shows spectral and chromatographic properties were identical to those of compound **59**.

Dimethyl (*R*)-2-((trifluoromethanesulfonyl)oxy)succinate (60).[215]

The procedure used for preparation of **61** was employed using **58** (0.296 g, 1.82 mmol), pyridine (0.170 mL, 2.10 mmol), and triflic anhydride (0.340 mL, 2.00 mmol), to give 0.481 g (90 % yield) of **60** as a yellowish oil. The spectral properties were identical to **61**.

Dimethyl (*S*)-2-((trifluoromethanesulfonyl)oxy)succinate (61).[245]

A solution of **59** (0.162 g, 1.00mmol) and pyridine (0.080 mL, 1.10 mmol) was added to a solution of triflic anhydride (0.170 mL, 1.00 mmol) in CCl_4 (10 mL) cooled in an ice-bath. The reaction mixture was stirred for 45 min. Hexane (3 mL) was added and the mixture was filtered through a plug of Na_2SO_4. The filtrate was concentrated *in vacuo* to furnish 0.264 g (89 % yield) of unstable oil **61**: IR (CH_2Cl_2 cast) 2962, 1771, 1753, 1441, 1422, 1380, 1286, 1244, 1224, 1215, 1209, 1177, 1143, 1030, 943, 857, 621 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 5.50 (t, 4.5 Hz, 1 H), 3.87 (s, 3 H), 3.05 (d, 4.5 Hz, 2 H); MS 145.0501 (145.0501 calcd for $C_6H_9O_4$, M^+ - OSO_2CF_3)

Dimethyl (*S*)-2-((benzyloxy)amino)succinate (62) [215]

A solution of **60** (0.531 g, 1.80 mmol) in dichloromethane (4 mL) was added to a solution of O-benzylhydroxylamine (0.300g, 2.43 mmol) in dichloromethane (6 mL), which was cooled in an ice-bath. The mixture was stirred for 17 h following which time, sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ether (3 x 20 mL). The ether layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified using flash chromatography [239] (30 % EtOAc/hexane) to give 0.421 g (87 % yield) of oil **62** : $[\alpha]_D$ = - 19.1° (c 1.5 $CHCl_3$) ; IR (CH_2Cl_2 cast) 1739, 1485, 1167 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (br s, 5 H), 6.25 (br s, 1 H), 4.68 (br t, 1 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 2.82 (dd, 3.0, 8.0 Hz, 1 H), 2.66 (dd, 3.7,

8.0 Hz, 1 H); exact mass 267.1102 (267.1106 calcd for $C_{13}H_{17}NO_5$). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.41; N, 5.24. Found : C, 58.31; H, 6.39; N, 5.17.

Dimethyl (*R*)-2-((benzyloxy)amino)succinate (63) [215]

This compound was prepared using triflate **61** and the procedure employed for conversion of triflate **60** to **62**. (*R*)-malic acid (0.135 g, 1.00mmol), pyridine (0.080 mL, 1.00 mmol) and triflic anhydride (0.170 mL, 1.00 mmol) were used for preparation of the triflate which was reacted with O-benzylhydroxylamine (0.251g, 2.04 mmol) to furnish 0.220 g (82 % yield) of **63**. The chromatographic and spectral properties were identical to those of **62**. $[\alpha]_D$ = + 19.1° (c 1.5 $CHCl_3$)

Phenyl diazomethane (64).[227, 228]

Benzaldehyde (21.6 g, 0.203 mol) was added dropwise to vigorously stirred hydrazine hydrate (20.0 g, 0.399 mol) cooled in an ice bath. The mixture was stirred for 2 h and was extracted with ether (3 x 40 mL). The ether extracts were dried ($MgSO_4$) and concentrated to ca. 50 mL. Dichloromethane (150 mL), and anhydrous $MgSO_4$ (20.0 g) were added followed by activated MnO_2 (45.0 g, 0.517 mol) in small (~ 2 g) portions. The mixture was stirred for 1 h and was filtered. The filtrate was concentrated, and the residual red oil was dissolved in pentane (100 mL). The pentane solution was cooled to - 78 °C and filtered at less than - 30 °C. The filtrate was concentrated and the red oil obtained was distilled under reduced pressure using a dry ice cold finger condenser. Dichloromethane

(30 mL) was added to the distillate to give a wine red solution. Titration of this solution against D - malic acid (1.34 g, 10.0 mmol) in 50% MeOH / $CHCl_3$ (25 mL) until the red colour persisted, showed that the solution was 3.5 M (34.1 mL, 58 % yield).

***N*-Benzyl-*p* -toluenesulfonamide (65).**[229]

p-Toluenesulfonyl chloride (95.05 g, 0.500 mmol) was added in small portions to a vigorously stirred solution of benzylamine (54.00 g, 0.500 mmol) in pyridine (50.00 g, 0.630 mmol). The mixture was stirred for 2 h and poured into ice-water (300 mL). The precipitate was filtered, washed with water, and recrystallised from boiling ethanol to give 97.96 g of white crystalline solid (70 % yield) **65** : mp 113-115 °C (lit [229] mp 114 °C);IR ($CHCl_3$ cast) 3269, 1423, 1323, 1310, 1176, 1167, 1059, 875, 754, 540 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) δ 7.82 - 7.72 (br d, 2 H), 7.36 - 7.14 (br s, 7 H), 4.64 (br s, 1 H), 4.12 (d, 3.0 Hz, 2 H), 2.44 (s, 3 H); exact mass 261.0828 (261.0824 calcd for $C_{14}H_{15}NO_2S$) .

***N*-Benzyl-*N* -nitroso-*p* -toluenesulfonamide [229] (66).**

Sodium nitrite (120.0 g, 75.0 mmol) was added in small (5 g) portions to a solution of **65** (21.0 g, 75.0 mmol) in 1: 4 glacial acetic acid /acetic anhydride (500 mL) cooled in an ice /salt bath (0 °C). The mixture was stirred overnight (18 h), poured into ice-water (200 mL), and was filtered. Recrystallisation from hot ethanol gave 18.4 g (80 % yield) of fine yellow needles **66**: mp 90 -92 °C (lit [229] mp 90 - 92 °C); IR ($CHCl_3$ cast) 1595, 1495, 1485, 1383, 1192, 665, 581 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.8

- 7.66 (br s, 2 H), 7.30 - 7.18 (br s, 5 H), 7.17 - 7.04 (m; 2 H), 4.91 (s, 2 H), 2.40 (s, 3 H); exact mass 290.0732 (290.0725 calcd for $C_{14}H_{14}N_2O_3S$)

Dibenzyl (*R*)-2-hydroxysuccinate (69).[228]

A solution of phenyldiazomethane (0.35 M in dichloromethane) was added to a solution of (*R*)-(+)- malic acid (0.672 g, 5.00 mmol) in 2:1 MeOH / $CHCl_3$ (15 mL) cooled in an ice-bath until a red tinge persisted. Glacial acetic acid (1 drop) was added and the mixture was concentrated *in vacuo*. Flash chromatography [239] (35 % EtOAc / Hexane) gave 1.48 g (93 % yield) of a colourless oil **69**: $[\alpha]_D$ = + 18.0 ° (c 2.0 $CHCl_3$); IR ($CHCl_3$ cast) 3450, 1737, 1263, 1212, 1166, 1092, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (br s, 10 H), 5.15 (s, 2 H), 5.08 (s, 2 H), 4.54 (q, 11.5, 4.5 Hz, 1 H), 3.30 (br s 1 H), 2.92 (dd, 16.0, 4.5 Hz, 1 H), 2.85 (dd, 16.0, 11.5 Hz, 1 H); exact mass 315.1233 (315.1233 calcd for $C_{18}H_{19}O_5$, MH^+); MS (CI NH_3) 332 (92 % $M^+ \cdot NH_4$). Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found : C, 68.79; H, 5.82.

Dibenzyl (*S*)-2-hydroxysuccinate (70).[228]

A solution of tetra -*N* -methylammonium hydroxide (9.10 mL, 20 % in hexane, 19.0 mmol) was added to a solution of (*S*)-(-)-malic acid (1.340 g, 10.0 mmol) in methanol (10 mL). The mixture was concentrated *in vacuo* and the white solid **68** was suspended in 3:1 dry DMF / acetonitrile (15 mL). Benzyl bromide (2.40 mL, 20.0 mmol) was added and the mixture was stirred for 21 h . Ether (150 mL) was added and the mixture was filtered. The filtrate was washed with water (3 x 50 mL), dried (Na_2SO_4), and

concentrated *in vacuo* . The residual yellow oil was purified using flash chromatography [239] (35 % EtOAc / Hexane) to afford 2.73 g (86 % yield) colourless, homogeneous oil **70**: The compound showed spectral properties and chromatographic behaviour similar to those of **69**.
$[\alpha]_D$ = - 19.3 ° (c 1.9 $CHCl_3$).

Dibenzyl (*R*)-2-((trifluoromethanesulfonyl)oxy)succinate (71).

A solution of **69** (1.57 g, 5.00 mmol) and pyridine (0.500 mL, 6.23 mmol) in dichloromethane (5 mL) was added to a solution of trifluoromethanesulfonic anhydride (0.900 mL, 5.34 mmol) in dichloromethane (10 mL) at - 20 °C (dry ice / CCl_4). The mixture was stirred at room temperature for 1 h. After three succesive additions of CCl_4 (3 x 10 mL) and concentration *in vacuo* to *ca.* 5 mL each time, the mixture was filtered through a plug of anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* to give 1.97 g (89 % yield) of an oil **71**: IR (CH_2Cl_2 cast) 1744, 1421, 1278, 1246, 1214, 1172, 1142, 1020, 936, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (br s, 10 H), 5.52 (t, 6.0 Hz, 1 H), 5.22 (s, 2 H), 5.14 (br d, 2 H), 3.08 (d, 6.0 Hz, 2 H); MS (CI, NH_3) 464 (100 % $M^+ \cdot NH_4$). Anal. Calcd for $C_{19}H_{17}F_3O_7S$: C, 51.12; H, 3.83. Found: C, 51.19; H, 3.79.

Dibenzyl (*S*)-2-((trifluoromethanesulfonyl)oxy)succinate (72)

The procedure for the preparation of **71** was used to convert **70** (1.571 g 5.00 mmol) to the triflate, except that the filtrate was concentrated on a rotary evaporator to give 2.211 g (99 % yield) of an oil **72**. The

spectral properties and chromatographic behavior were similar to those of 71.

Dibenzyl (*S*)-2-((benzyloxy)amino)succinate (73).

A solution of 71 (0.391 g, 0.884 mmol) in dichloromethane (6 mL) was added to a solution of O-benzylhydroxylamine (0.135 g, 1.10 mmol) in dichloromethane (6 mL) cooled in an ice bath. The mixture was stirred for 17 h, then sat. aq. $NaHCO_3$ (5 mL) was added. The mixture was extracted with ether (3 x15 mL), the ether extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography [239] (25 % EtOAc / Hexane) gave 0.280 g (66 % yield) of white crystalline solid **73**: mp 60 - 62 °C; $[\alpha]_D$ = - 8.12 ° (c 1.58 $CHCl_3$); IR ($CHCl_3$ cast) 1737, 1498, 1455, 1280, 1262, 1212, 1162, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 - 7.20 (br s, 15 H), 6.50 - 5.98 (br s, 1 H), 5.16 (br d, 2 H), 5.08 (s, 2 H), 4.72 (s, 2 H), 4.10 (dd, 6.0, 7.5 Hz, 1 H), 2.90 (dd, 16.5, 6.0 Hz, 1 H), 2.74 (dd, 16.5, 7.5 Hz, 1 H); exact mass 419.1711 (419.1732 calcd for $C_{25}H_{25}NO_5$); MS (CI NH_3) 420 (100 % M^+;H). Anal. Calcd. for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.00; N, 3.33. Found: C, 71.36; H, 5.96; N, 3.43.

Aspartic acid 74 from 73.

A solution of **73** (0.140 g, 0.334 mmol) in 5.7 M HCl (5 mL) was hydrogenolysed [118] under slightly (10 mm of Hg) positive hydrogen pressure using 5 % Pd/C (0.015 g) as a catalyst. The mixture was filtered, H_2S gas was passed through the filtrate, and the resulting mixture was filtered. The filtrate was lyophilised to give 0.028 g (58 % yield) of a white

solid **74**. The chromatographic behaviour and spectral properties were similar to those of an authentic sample of aspartic acid. For **74**: IR (KBr) 3400 - 2800, 1668, 1857, 1608, 1512, 1422, 1358, 1335, 1299, 1247, 1151, 1119, 1079, 1040, 988, 934, 898, 776 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 3.95 (q, 4.4, 7.6 Hz, 1 H), 2.92 (dd, 4.4, 17.6 Hz, 1 H), 2.79 (dd, 7.6, 17.6 Hz, 1 H); MS (Glycerol / HCl pos FAB) 134 ($M^{+\bullet}H$)

Standard camphanamide dimethylester 75 from L-aspartic acid.

The procedure [93,233, 234] used to transform **56** to **57** was employed except that the methyl camphanoate in the product was removed by sublimation at 70 °C at 0.25 torr. L-Aspartic acid (66.2 mg, 5.00 mmol) and (*R*)-camphanoyl chloride (0.216 g, 1.00 mmol) were used to give 0.025 g (14 % yield) of an oil **75**: IR (CH_2Cl_2 cast) 3280, 2960, 1792, 1743, 1678, 1525, 1440 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 - 7.20 (br d, 1 H), 4.91 - 4.83 (m, 1H), 3.78 (s, 3 H), 3.68 (s, 3 H), 3.02 (dd, 5.0, 16.0 Hz, 1 H), 2.89 (dd, 16.0, 5.0 Hz, 1 H), 2.60 - 2.40 (m, 1 H),2.04 - 1.84 (m, 2 H) 1.78 - 1.60 (m, 1 H),1.11(s, 3 H), 1.08 (s, 3 H), 0.86 (s, 3 H); exact mass 341.1471 (341.1475 calcd for $C_{16}H_{23}NO_7$).

Standard mixture of camphanamide dimethyl esters 75 and 76 from DL-aspartic acid.

The standard mixture was prepared using the procedure [93, 233, 234] employed for preparation of **75**. DL-Aspartic acid (0.0668 g, 0.500 mmol) and camphanic acid chloride (0.216 g, 1.00 mmol) were used and 0.019 g (11 % yield) of the camphanamide dimethyl esters was obtained. Although

the two diastereomers show similar chromatographic behaviour (TLC, GC), the 2 R (D) isomer can be clearly seen by ^{1}H NMR by the resonances of the ester methyl groups at δ 3.75 (s, 3 H) and 3.71 (s, 3 H).

Camphanamide of dimethyl aspartate from aspartic acid 74.

Aspartic acid **74** (0.010 g, 0.058 mmol) obtained from **73** by hydrogenolysis was converted using the same procedure to give 0.0091 g (47 % yield) of camphanamide derivative. The ^{1}H NMR (200 MHz, $CDCl_3$) showed that the mixture contains ~3.2 % of the 2*R* diastereomer.

Dimethyl 2-methoxysuccinate (77).[245]

A solution of **61** (0.271 g, 0.890 mmol) in methanol (2 ml) was added to a solution of *tert*-butyl N-hydroxycarbamate (0.134 g, 1.00 mmol) and potassium hydroxide (0.660 g, 85 %, 1.00 mmol) in methanol (4 ml). The mixture was stirred for 12 h, poured into pH 7 phosphate buffer, and concentrated *in vacuo*. The residue was extracted with ether (3 x 20 mL). The ether layers were dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography [239] (25 % EtOAc/hexane) gave 0.076 g (48 % yield) of **77** as colorless oil [245] : IR (CH_2Cl_2 cast) 1740, 1438, 1273, 1218, 1170, 1098 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.21 (q, 5.2, 7.2 Hz, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.44 (s, 3 H), 2.82 (dd, 5.4, 16.4 Hz, 1 H), 2.70 (dd, 7.2, 16.4 Hz, 1 H); MS (CI NH_3) 194 ($M^{+\bullet}NH_4$).

Dimethyl 2-[((*tert* -butyloxycarbonyl)amino)oxy]succinate (78).

Triflate **61** was prepared using **59** (0.164 g, 1.00 mmol), pyridine (0.080 mL, 1.00 mmol), and triflic anhydride (0.170 mL, 1.00 mmol). Triflate **61** thus prepared was dissolved in dichloromethane (4 mL) and added to a solution of *tert* - butyl-*N* -hydroxy carbamate (0.135 g,1.00 mmol) and finely divided potassium carbonate (0.198 g, 2.00 mmol) in dichloromethane (6mL). The mixture was stirred for 16 h and filtered through Na_2SO_4 and celite 545. The filtrate was evaporated and the residue was purified on flash chromatography [239](45% EtOAc / Hexane) to give **78** as an oil (0.076 g, 27 %): IR (CH_2Cl_2 cast) 1745, 1368, 1247, 1167 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1 H), 4.75 (t, 5.9 Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 2.91 (d, 5.9 Hz, 2 H),1.47 (s, 9 H) ; MS (CI NH_3) 295 ($M^+ \cdot NH_4$): Anal. Calcd for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.90; N, 5.05. Found : C, 47.48; H, 6.93; N, 4.97.

Dibenzyl (*R*)-2-[((*tert* -butyloxycarbonyl)amino)oxy]succinate (80) and Dibenzyl fumarate (81).[247]

Lithium *tert* -butyl-*N* -hydroxycarbamate **79** (0.127 g, 1.00 mmol) (prepared from reaction of *tert* -butyl-*N* -hydroxycarbamate and LiOH in 1:1:1 MeOH / H_2O / THF followed by lyophilisation) was added to a solution of **72** (0.410 g, 0.927 mmol) in dry dichloromethane. THF (10 mL) was added and the mixture was stirred for 18 h. Sat. aq. $NaHCO_3$ (15 mL) was added and the mixture was extracted with ether (3 x15 mL). The ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* . The residue was purified by flash chromatography [239] (28 % EtOAc/Hex) to give a white solid **81** and colorless gum **80**.

For **80** : $[\alpha]_D$ = + 28.4 ° (c 1.7 $CHCl_3$); IR (CH_2Cl_2 cast) 3260, 1743, 1456, 1386, 1267, 1248, 1165, 1113, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (br s, 1 H), 7.34 (br s, 10 H), 5.18 (s, 2 H), 5.12 (s, 2 H), 5.82 (t, 6.0 Hz, 1 H), 2.97 (dd, 6.0, 16.5 Hz, 1 H), 2.92 (dd, 6.0, 16.5 Hz, 1 H), 1.48 (s, 9 H); MS (NH_3 CI) 447 ($M^+ \cdot NH_4$); Anal. Calcd. for $C_{23}H_{27}NO_7$: C, 64.32 ; H, 6.33 ; N, 3.26 . Found: C, 64.28 ; H, 6.40 ; N, 3.13.

For **81**: mp 60 - 62 °C ; IR ($CHCl_3$ cast) 1709, 1456, 1379, 1293, 1149, 754, 688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38 (br s, 10 H), 6.94 (s, 2H); exact mass 296.1053 (296.1049 calcd for $C_{18}H_{16}O_4$).

Dibenzyl (*S*)-2-[((*tert*-butyloxycarbonyl)amino)oxy]succinate (82).

Lithium *tert*-butyl-*N*-hydroxycarbamate (0.695 g, 5.00 mmol) was added to a solution of **71** (2.161 g, 4.88 mmol) in dichloromethane (15 mL) cooled in an ice bath. Dry DMF (5 mL) was added and the mixture was stirred for 2 h at room temperature. The reaction was terminated by addition of sat. aq. NH_4Cl (5 mL) and water (5 mL). The product was extracted with ether (3 x 35 mL), and the ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* . The residual yellow oil was purified by flash chromatography [239](28 % EtOAc/Hexane) to give 1.351 g (62 % yield) of colorless gum **82** along with 0.238 g (16 % yield) of **81**.

82 : $[\alpha]_D$ = - 28.9 ° (c 1.6 $CHCl_3$); All other chromatographic and spectral properties were similar to those of **80**.

(*R*)-2-[((*tert*-Butyloxycarbonyl)amino)oxy]succinic acid (83).

A solution of **80** (1.509 g, 3.51 mmol) in EtOAc (10 mL) was hydrogenolysed using 5 % Pd / C (0.102 g) as a catalyst, under ~15 torr of hydrogen pressure in excess of 1 atmosphere, until the absorption of H_2 ceased (1.5 h). The mixture was filtered through a celite 545 pad and concentrated *in vacuo* to give 0.840 g (95 % yield) of white foam **83**, which required no further purification: mp 71 - 74 °C; $[\alpha]_D$ = + 36.4 ° (c 3.2 $CHCl_3$); IR (CH_2Cl_2 cast) 3220, 2083, 2938, 1720, 1396, 1371, 1256, 1162, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 4.76 (dd, 3.5, 9.2 Hz, 1 H), 3.18 (dd, 3.5, 18.0 Hz, 1 H), 2.92 (dd, 9.2, 18.0 Hz, 1 H), 1.50 (s, 9 H); exact mass 249.0849 (249.0849 calcd for $C_9H_{15}NO_7$); MS (CI NH_3) 267 (87 % $M^+ \cdot NH_4$).

(*S*)-2-[((*tert* -Butyloxycarbonyl)amino)oxy]succinic acid (84).

The procedure used to prepare **83** from **80** was employed to convert **82** (1.101 g, 2.56 mmol) to 0.591 g (99 % yield) of **84**. The compound showed similar spectral properties to those of **83**. $[\alpha]_D$ = - 35.1 ° (c 3.3 $CHCl_3$).

(*R*)-2-[(Amino)oxy]succinic acid, hydrochloride (85) [152]

Distilled 5.7 M aq. HCl (5 mL) was added to a solution of **83** (0.765 g, 3.072 mmol) in THF (5 mL), and the mixture was stirred for 2 h. The mixture was extracted with ether (3 x 15 mL) and the aqueous layer was lyophilised to give 0.552 g (96 % yield) of a hygroscopic white foam **85**: $[\alpha]_D$ = + 56.5 ° (c 1.2 H_2O); IR (KBr) 3420, 3200-2800, 3000, 2680, 1372, 1420, 1188, 1045 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 4.88 (br dd, 1 H), 3.06 (dd,

4.0. 17.6 Hz, 1 H), 2.94 (dd, 17.6, 7.0 Hz, 1 H); MS (Glycerol / HCl pos FAB) 150 (M^{+}•H, 100 %) . Anal. Calcd. for $C_4H_8ClNO_5$: C, 25.89 ; H, 4.31 ; N, 7.54 . Found: C, 25.53 ; H, 4.43 ; N, 7.40.

(*S*)-2-[(Amino)oxy]succinic acid, hydrochloride (86). [152]

The procedure used to prepare **85** was employed for transformation of **84** (0.511 g, 2.05 mmol) to 0.373 g (97 % yield) of white foam **86**. The material shows spectral properties similar to those of **85**.$[\alpha]_D$ = - 58.9 ° (c 1.98 H_2O).

Dimethyl (*R*)-malate (87) from 85.

A solution of **85** (0.056 g, 0.302 mmol) in 5.7 M HCl (2 mL) was hydrogenolised in the presence of PtO_2 (0.002 g) under ~ 5 torr pressure in excess of 1 atmosohere of hydrogen gas, for 16 h. The mixture was filtered through a celite pad and the filtrate was lyophilised to give a white solid. The solid was dissolved in 1:2 $CHCl_3$ / MeOH (4 mL), and a solution of diazomethane in ether was added until a slight yellow color persisted. The solution was concentrated *in vacuo*. The residue was dissolved in chloroform, and the chloroform solution was filtered through a short silica gel column. The filtrate was concentrated *in vacuo* to give 0.045 g (92 % yield) of a colorless oil **87**. The chromatographic behaviour and spectral properties are similar to those of **59**.

Dimethyl (*S*)-malate (88) from 86. [244]

The procedure used to prepare **87** was employed to convert **86**

(0.027 g, 0.146 mmol) to 0.023 g (97 % yield) of the dimethylester **88**. The spectral and chromatographic properties were similar to those of **87** and **59**.

Standard mixture of dimethyl (2*S*, 2'*S*)-2-[((2-methoxy-2-trifluoromethyl)-2-phenylacetyl)oxy]butanedioate (89) and its 2R diastereomer 90. [236, 237, 246]

The standard mixture was prepared using a mixture of 0.048 g of malic acids containing 38.5 % of D-malic acid and 61.4 % L-malic acid to give the MTPA ester in 58 % yield (see procedure below). The two diastereomers could be clearly distinguished by ^{1}H NMR. Injection of the crude mixture as well as the mixture purified using preparative TLC, on Alltech 8011/2 bonded FSOT (polyphenylsiloxane) 10 m x 0.53 mm GC column at 160 ° for 2 min, 2 °C /min to 190 ° with 6.2 psi He at 160 ° showed two peaks with R_{tS} = 15.06 min (S) and R_{tR} = 15.41 (R) min. The ratios calculated from the chromatogram were within ± 0.2 % of the actual ratios. MTPA ester independently prepared from L-malic acid showed a peak at R_t = 15.02'.

MTPA Ester 89. [236, 237, 246]

A solution of DCC (0.018 g, 0.087 mmol) in dichloromethane (0.5 mL) was added to a solution of (*S*)- (-)-2-methoxy-2- trifluoromethyl phenylacetic acid (MTPA) (0.020 g, 0.087 mmol) and *S*-malic acid , dimethylester **88** (0.014 g, 0.087 mmol) in dichloromethane (1 mL). A crystal of dimethylaminopyridine (DMAP) (~ 0.001 g) was added and the mixture was stirred for 24 h. It was concentrated *in vacuo* . Ether (1 mL) was

added and the mixture was passed through a short silica gel column , us ether as eluent (10 mL). The filtrate was evaporated to give 0.055 g colourless oil. A small portion of this mixture (0.019 g) was purified using preparative layer TLC (30 % EtOAc / hexanes) to give 0.005 g of white solid (yield 44 %) 89: IR ($CHCl_3$ cast) 1751, 1622, 1438, 1270, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.58 (br s, 2 H), 7.44 - 7.38 (br s, 3 H), 5.72 (q, 8.8, 4.0 Hz, 1 H), 3.81 (s, 3 H), 3.63 (br d, 3 H), 3.58 (s, 3 H), 2.95 (dd, 16.8, 4.0 Hz, 1 H), 2.87 (dd, 16.8, 8.8 Hz, 1 H); exact mass 378.0919 (378.0927 calcd. for $C_{16}H_{17}F_3O_7$); MS (CI NH_3) 396 ($M^+ \cdot NH_4$, 100 %)

The enantiomeric purity was determined to be 96.3 ±0.2 % . The GC and the NMR estimations were in good agreement within experimental limitations.

MTPA Ester 90. 236, 237, 246

The procedure used for the preparation of **89** was employed to convert **87** (0.007 g, 0.042 mmol) to **90** in 41 % yield. The compound showed similar spectral and chromatographic (TLC) behavior to those of **89**, but could be separated from **89** using GC (*vide supra*) and could be clearly observed by ^1H NMR due to differences in the chemical shifts of the methyl ester and methoxy protons.

90 : ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.56 (br s, 2 H), 7.26 - 7.18 (br s, 3 H), 5.71 (q, 4.0, 8.0 Hz, 1 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.56 (br d, 3 H), 3.01 (dd, 16.8 Hz, 4.0 Hz, 1 H), 2.88 (dd, 16.8, 4.0 Hz, 1 H).

The determined enantiomeric purity was 88.2 ±0.2 %. The GC and the NMR estimations were in good agreement within experimental limitations.

Dibenzyl carbonate (93).[238]

Butyllithium (35.0 mL, 1.44 M in hexanes, 50.0 mmol) was added over 10 min to a solution of benzyl alcohol (5.17 mL, 50.0 mmol) in dry THF (20 mL) cooled to - 78 °C (dry ice / acetone). The alkoxide solution was transfered to a solution of benzyl chloroformate (7.13 mL, 50.0 mmol) in dry THF cooled to - 78 °C, using a canula. The mixture was warmed to room temperature, and water (50 mL) and ether (150 ml) were added. The ether layer was washed with sat. aq. $NaHCO_3$ (25 mL) and water (3 x 25 mL) and was dried (Na_2SO_4). Concentration of the ether layer gave a yellow oil which was fractionally distilled under reduced pressure to give 10.24 g (84 % yield) of colourless oil **93**: bp 162 - 164 °C at 1 torr (lit [238] bp 157 ° at 1.1 torr); IR ($CHCl_3$ cast) 1745, 1498, 1457, 1390, 1264, 948, 908, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36 (br s, 10 H), 5.17 (s, 4 H); MS (CI NH_3) 260 (100 % $M^{+}{\cdot}NH_4$).

Benzyl carbazate (94).[238]

Hydrazine hydrate (5.60 g, 100 mmol) was added to a solution of **93** (12.10 g, 50.0 mmol) in ethanol (25 mL) cooled in an ice bath. The solution was refluxed for 45 min and concentrated *in vacuo* . The residual yellow oil was dissolved in 1:1 ethyl acetate/ether (75 mL) and washed with 10 % aq. NH_4Cl solution (3 x 25 mL). The combined organic layers were dried.

(Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from hot ether to give 4.81 g (57 % yield) of white needles **94** : mp 69 - 70 °C (lit [238] mp 60 -65 °C); IR ($CHCl_3$ cast) 3333, 3303, 1688, 1651, 1292, 1085, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (br s, 5 H), 6.01 (br s, 1 H), 5.14 (s, 2 H), 3.79 (br d, 2 H); exact mass 166.0744 (166.0742 calcd for $C_8H_{10}N_2O_2$).

Dibenzyl (*S*)-2-[(((benzyloxy)carbonyl)amino)amino]succinate (95).

Benzyl carbazate (1.662 g, 10.0 mmol) was added to a solution of **71** (2.211 g, 4.95 mmol) in dichloromethane (10 mL) and the mixture was stirred for 24 h. Water (5 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and the mixture was extracted with ether (3 x 35 mL). The ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* . The residual yellow oil was purified using flash chromatography [239] (45 % EtOAc / hexane) to give 2.071 g (89 % yield) of a colourless oil **95**: $[\alpha]_D$ = - 7.48 ° (c 2.0 $CHCl_3$); IR ($CHCl_3$ cast) 3320, 1735, 1488, 1455, 1262, 1167, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (br s, 15 H), 6.6 (br s, 1 H), 5.10 (s, 2 H), 5.08 (s, 2 H), 5.04 (s, 2 H), 4.98 (t, 5.5 Hz, 1 H), 2.88 (d, 5.5 Hz, 2 H); exact mass 462.1791 (462.1791 calcd for $C_{26}H_{26}N_2O_6$); MS (CI NH_3) 463 (M^+•H). Anal. Calcd. for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.66; N, 6.05 . Found: C, 67.38; H, 5.70; N, 5.93.

Dibenzyl (*R*)-2-[(((benzyloxy)carbonyl)amino)amino]succinate (96).

The procedure used to prepare **95** was employed. Compound **72** (0.331 g, 0.742 mmol) was treated with **94** to give 0.335 g (97 % yield) of **96**: The chromatographic and spectral properties of this compound were similar to those of **95**. $[\alpha]_D$ = + 7.7 ° (c 2.0 $CHCl_3$).

(*S*)-2-[(Amino)amino]succinic acid, monohydrate (91). [161, 162]

A solution of **95** (1.00 g, 2.16 mmol) in 10 % AcOH / EtOAc (10 mL) was hydrogenolysed under ~ 60 torr pressure of hydrogen gas in excess of 1 atmosphere using 5 % Pd/C (0.100 g) as a catalyst for 8 h. The mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo* . The resultant white solid was recrystallised from THF / water to give 0.191 g (52 % yield) of white needles **91**: mp 116 - 118 °C; $[\alpha]_D$ = - 14.2 ° (c 1.0 H_2O) (lit.[160] $[\alpha]_{578}$ = -14.2 ° (c 1.0 H_2O)) ; IR (KBr) 3418, 3268, 1755, 1480, 1320, 1297, 1264, 1244, 804, 656, cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 3.95 (dd, 6.8, 4.8 Hz, 1 H), 2.97 (dd, 4.8, 16.6 Hz, 1 H), 2.85 (dd, 6.8, 16.6 Hz, 1 H); MS (Glycerol / HCl pos FAB) 149 (M^+•H). Anal. Calcd. for $C_4H_{10}N_2O_5$: C, 28.91; H, 6.06; N, 16.86. Found: C, 28.82; H, 6.16; N, 16.93.

(*R*)-2-[(Amino)amino]succinic acid, monohydrate (92)[161, 162]

The procedure used for hydrogenolysis of **95** to **91** was used. Hydrogenolysis of 0.504 g (1.09 mmol) of **96** gave 0.124 g (74 % yield) of white needles **92**: $[\alpha]_D$ = + 14.3 ° (c 1.5 H_2O) (lit.[162] $[\alpha]_{578}$ = 14.2 ° (c 1.0 H_2O)); The compound showed spectral and chromatographic properties similar to those of **91**.

L-Aspartic acid 97 from 91.

A solution of **91** (0.0148 g, 0.100 mmol) in water (5 mL) and acetic acid (1 drop) was hydrogenolysed over PtO_2 (0.004 g) util the TLC (1:1:1 butanol /AcOH / water, silicagel Merck F254) showed no spots for the hydrazino compound with p-dimethylaminobenzaldehyde / HCl spray (10 h). The mixture was filtered through a celite pad and the filtrate was lyophilised to give 0.0131 g (quantitative yield) of white solid **97** . The compound was chromatographically and spectroscopically similar to that of authentic aspartic acid and **74**.

D-Aspartic acid 98 from 92.

The procedure [93,233, 234] used for preparation of **97** from **91** was used. Compound **92** (0.0151 g, 0.100 mmol) was hydrogenolised to give 0.130 g (quantitative yield) of white solid **98**. The spectral and chromatographic properties were identical to those of an authentic sample of aspartic acid.

Camphanamide dimethyl ester 99 from 97.

The procedure [233, 234] previously used for preparation of **75** was employed. Compound **97** (0.0134 g, 0.100 mmol) was transformed to give 0.00361 g (10 % yield) of **99**. The ^1H NMR (400 MHz, $CDCl_3$) shows no trace of the 2 *R* diastereomer. The spectral and chromatographic properties were similar to those of **75** prepared above.

Camphanamide dimethylester 100 from 98.

The procedure used for preparation of **75** was employe . Compound **98** (0.0121 g, 0.0909 mmol) was transformed to give 0.00350 g (11 % yield) of **100**: IR (CH_2Cl_2 cast) 3280, 2960, 1792, 1743, 1678, 1525, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.2 (br d, 1 H), 4.91 - 4.83 (m, 1H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.02 (dd, 5.0, 16.0 Hz, 1 H), 2.89 (dd, 16.0, 5.0 Hz, 1 H), 2.60 - 2.40 (m, 1 H),2.04 - 1.84 (m, 2 H), 1.78 - 1.60 (m, 1 H),1.11(s, 3 H), 1.08 (s, 3 H), 0.86 (s, 3 H); exact mass 341.1471 (341.1475 calcd for $C_{16}H_{23}NO_7$). The ^1H NMR (400 MHz, $CDCl_3$) shows no trace of the 2 *S* diastereomer.

Using standards prepared from authentic L- and DL-aspartic acids and using ^1H NMR (400 MHz), it was possible to detect even 0.5 % of one diastereomer in the presence of other.

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Appendix

The enzymological studies described below were performed by Dr. Monica Palcic (Food Science, University of Alberta) and co-workers. Aspartate α-decarboxylase was isolated [248-251] from *E. coli* in PK_1 and PK_2 form and Commercially available aspartate aminotransferase [252] (EC 2.6.1.2) were tested for inhibition by both enantiomers of α-hydrazino succinate **91** and **92** and both enantiomers of α-oxyaminosuccinate **85** and **86**.

Aspartate α-Decarboxylase:

- Pyruvoyl dependent enzyme
- Two forms PK_1 and PK_2
- PK_2 major protein by electrophoresis
- K_m for PK_1 enzyme 388 μM
- K_m for PK_2 enzyme 185 μM

Table 3: Results of inhibition studies using PK_1 form

Inhibitor		K_i	type of inhibition
L-oxyaminosuccinate	**86**	-	-
D-oxyaminosuccinate	**85**	640 μM	irreversible
L-hydrazinosuccinate	**91**	-	-
D-hydrazinosuccinate	**92**	214 μM	competitive

Table 4: Results of inhibition studies using PK_2 form

Inhibitor		K_i	type of inhibition
L-oxyaminosuccinate	86	263 µM	competitive
D-oxyaminosuccinate	85	46 µM	competitive
L-hydrazinosuccinate	91	-	-
D-hydrazinosuccinate	92	61.2 µM	competitive

Table 5: Results of inhibition studies using aspartate aminotransferase (PLP dependent enzyme) K_m = 400 µM

Inhibitor		K_i	type of inhibition
L-oxyaminosuccinate	86	≤ 0.0002 µM	competitive
D-oxyaminosuccinate	85	≤ 0.002 µM	competitive
L-hydrazinosuccinate	91	0.0002 µM	competitive
D-hydrazinosuccinate	92	0.003 µM	competitive

The inhibition observed for the D-oxyamino succinate may be due to the 11 % of the L-isomer present in the compound. Studies [160 - 163] by Yamada and co-workers using aspartate aminotransferase (EC 2.6.1.1) and hydrazino succinates also show that the compounds are slow, tight-binding inhibitors of the enzyme.