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THE UNIVERSITY OF ALBERTA

New Methods for Synthesis of β-Substituted α-Amino Acid Derivatives

by

Sunil Vasant Pansare

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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Date: February 6, 1989

To my parents

Abstract

A synthesis of unprotected aliphatic α-amino acids bearing fluorine at the β-position has been developed. The enolate of a benzyl glycinate derivative in which the nitrogen is protected as a 4,5-diphenyl-4-oxazolin-2-one moiety, reacts at low temperature (-130 °C) with aldehydes to afford the corresponding β-hydroxy amino acid derivatives in good yield (55-90%) with a 5:1 diastereomeric ratio (allo/threo). These β-hydroxy compounds react with (diethylamino)sulfur trifluoride (DAST) to form the corresponding β-fluoro derivatives in approximately 1:1 diastereomeric ratio and/or the corresponding elimination products. Deprotection of the β-fluoro compounds by hydrogenolysis (45 psi H_2, Pd/C) gives the free β-fluoro α-amino acids in 88-99% yield. The sequence works well for analogues of amino acids having aliphatic side chains, but attempted fluorination of protected β-hydroxy amino acids possessing functionalized chains gives elimination products instead of the β-fluoro compounds.

A synthesis of the amino acid proline and its analogues, through the intermediacy of N-modified serine β-lactones was investigated. The requisite N-(2-(benzenesulfonyl)ethyl) -N-(benzyloxycarbonyl)-L-serine β-lactone was synthesized from the corresponding N-protected serine and its intramolecular cyclization was investigated. The cyclization proceeds by attack at the carbonyl carbon of the lactone to afford a 2-hydroxymethyl-3-oxopyrrolidine derivative. Attack at the β-carbon was not observed.

The synthesis and nucleophilic ring opening of optically pure N-protected α-amino-β-alkyl-β-lactones was examined. Treatment of N-*tert*-butoxycarbonyl (Boc) L-threonine under a variety of conditions leading to carboxyl group activation did not produce any of the desired β-lactone. Reaction of N-(benzenesulfonyl)-L-threonine under modified Mitsunobu conditions (Ph_3P, dimethyl azodicarboxylate, -78 °C) gives decarboxylative elimination to afford the corresponding N-protected aminopropenes. However N-(benzenesulfonyl)-L-threonine and other N-(benzenesulfonyl)-β-hydroxy amino acids

cyclize to the corresponding chiral β-lactones in 40-55% yield using carboxyl group activation by 4-bromobenzenesulfonyl chloride in pyridine. Nitrogen (pyrazole, benzylamine), oxygen (hydroxide, acetate), and carbon (EtMgCl, $CuBr{\cdot}SMe_2$) nucleophiles prefer to attack these lactones at the carbonyl carbon, in contrast to their reactions with β-butyrolactone and serine β-lactones. However these β-lactones are opened at the β-carbon with inversion of configuration by some sulfur (thiourea) and halogen (magnesium halides) nucleophiles to N-protected optically pure β-substituted amino acids in good yield.

Acknowledgements

I am most grateful to my supervisor Dr. John C. Vederas for his help, support and encouragement during my studies. I thank all the members of our research group for helpful discussions: especially Dr. Paul Harrison, Mr. Y. H. Song, and Dr. Laird Trimble for their help on several occasions. The staff in spectral and analytical services in the Department of Chemistry is gratefully acknowledged for their assistance in characterizing compounds. Finally, I would like to thank my wife, Jyoti, for her patience and support during this work and for typing this manuscript.

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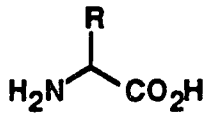
List of Abbreviations

Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
iBu	isobutyl
cat.	catalytic
Cbz	benzyloxycarboryl
DAST	(Diethylamino)sulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*, *N'*-Dicyclohexylcarbodiimide
DMAD	Dimethyl azodicarboxylate
DMAP	*N*, *N'*-Dimethylaminopyridine
DMF	*N*, *N'*-Dimethylformamide
EDTA	Ethylenediaminetetraacetic acid
Et	ethyl
Enz	enzyme
FAB	fast-atom bombardment
IR	infrared spectroscopy
LDA	Lithium diisopropylamide
Me	methyl
MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
NBA	*N*-Bromoacetamide

NMR	nuclear magnetic resonance
OP	OPO_3H^-
Ph	phenyl
PLP	Pyridoxal phosphate
nPr	propyl
iPr	isopropyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
THF	Tetrahydrofuran
TLC	thin layer chromatography
Ts	p-toluenesulfonyl

Introduction

A large number of α-amino acids (several hundred) have been discovered in Nature.[1] Of this diverse group of biologically important molecules the 20 common L-α-amino acids play an important role in the primary metabolism of all living organisms and are constituents of proteins and peptides indispensable for life. The non-protein amino acids occur in either free form or as parts of larger molecules in Nature, and are responsible for a wide spectrum of biological activities.[1-3] In addition to their fundamental biochemical and physiological significance, amino acids play an important role in human and animal nutrition and have gained commercial importance as sweetners, flavourings, and taste enhancers[4] and also as components of many therapeutic agents, agrochemicals and cosmetics. Some amino acids are valuable tools to elucidate enzymatic reaction mechanisms.[5,6] Due to the wide spectrum of applications of amino acids, the construction of these compounds has been of interest to chemists for a long time,[7] and considerable effort has been devoted to both achiral[8-12] and enantioselective[13-29] synthesis of them. In addition to the synthesis of known and novel amino acids, there has also been an interest in the preparation of analogues like β-fluoro-α-amino acids[30-41] due to their ability to function as mechanism based irreversible inactivators of certain enzymes and thereby block important metabolic pathways.[42-47]



α - amino acid

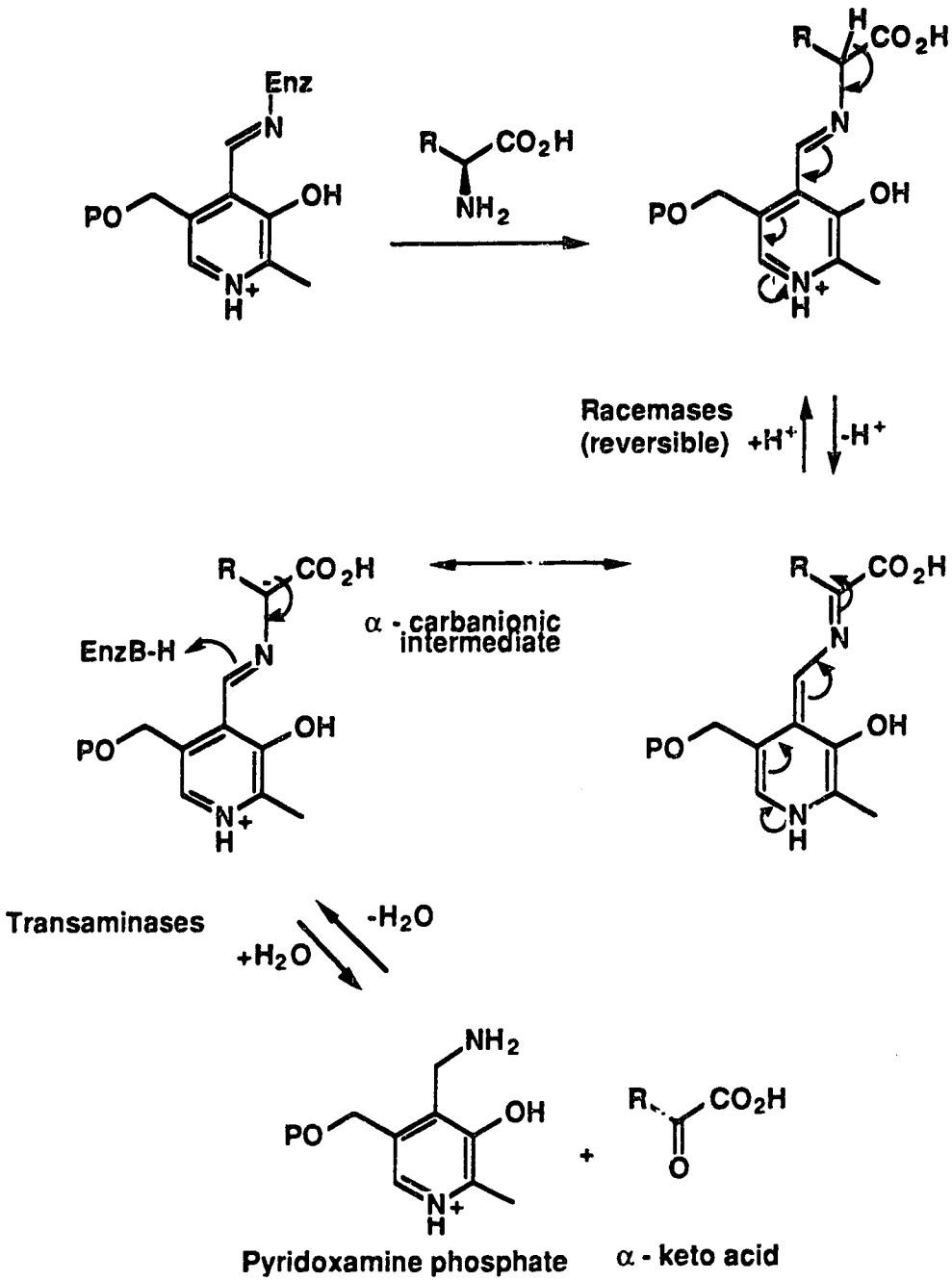
β - fluoro α - amino acid

One of the objectives of this research was the development of a general synthesis of β-fluoro-α- amino acids bearing the β-fluorine directly on the parent side chain. Such

species and their analogues (e. g. α-difluoromethyl amino acids) have been shown to possess considerable chemotherapeutic potential. For example, alanine racemase, an enzyme which provides D-alanine for bacterial cell wall formation is inactivated by β-fluoroalanine and its analogues,[48,49] and β-fluoroasparagine inhibits the growth of certain human leukemic cells in culture.[50] An ornithine analogue, α-difluoromethylornithine, is an irreversible inactivator of ornithine decarboxylase and has been shown to cure trypanosomiasis in mice.[51] α-Fluoromethyl histidine,[52] an inactivator of histidine decarboxylase, has potential use in the treatment of allergy, hypersensitivity, gastric ulcer, and inflammation by controlling histamine levels in the animal body.

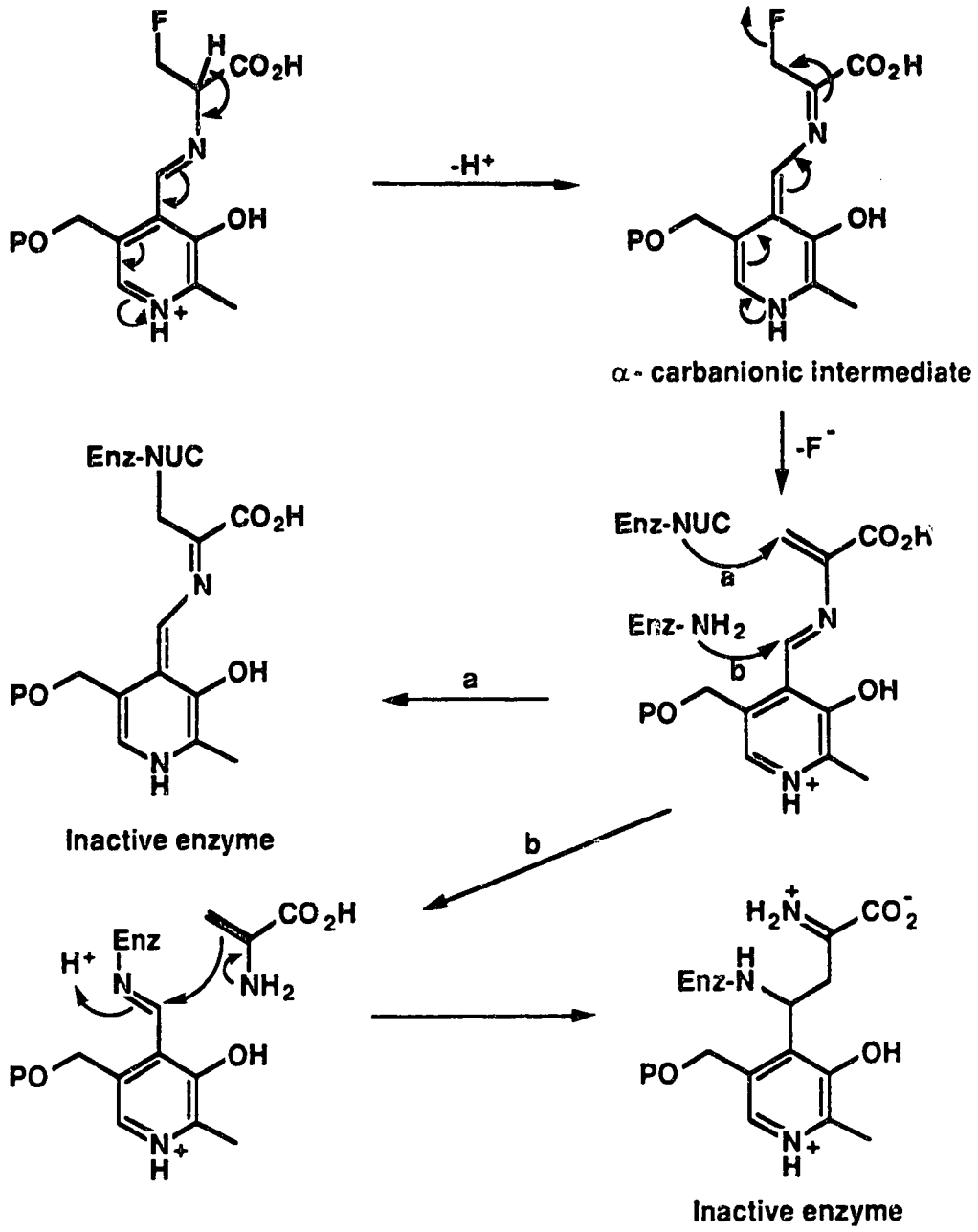
In amino acid metabolism a variety of functions are performed by pyridoxal phosphate (PLP) dependant enzymes.[53] The catalytic mechanism of these enzymes has been extensively studied.[54,55] The PLP cofactor facilitates chemistry at the α-carbon of amino acid substrates by stabilizing α-carbanion equivalents thereby lowering energy barriers for catalysis. Two categories of enzymes, racemases and transaminases, begin catalysis by cleavage of the α-carbon-hydrogen bond in amino acids and are targets for mechanism based inactivation by β-fluoro-α-amino acids, which function as enzyme-activated irreversible inhibitors or "suicide substrates".[42-47] The general mechanism for racemases and transaminases (Figure 1) is as follows. The PLP cofactor occurs as an imine adduct with the ε-amino group of an active site lysine residue,[54] and transimination occurs with the α-amino group of the amino acid substrate. The protonated pyridine ring now acts as an electron sink and α-hydrogen loss takes place, to produce an "α-carbanionic" intermediate. In epimerization, reprotonation of the α-carbon on the opposite face and hydrolysis generates the epimeric amino acid. In transamination, tautomerisation followed by hydrolysis of the resulting ketimine gives an α-keto acid and pyridoxamine phosphate.[54]

Figure 1. Mechanism of PLP-dependant racemases and transaminases.



The mechanism by which β-fluoro-α-amino acids inhibit these processes has been proposed [46] to proceed as shown in Figure 2.

Figure 2. Proposed mechanism of inactivation of PLP-dependant enzymes by fluorinated substrate analogues.



In the presence of a leaving group at the β position (fluorine in the β-fluoro-α-amino acids) the "α-carbanionic" intermediate can undergo elimination. This generates an electrophilic olefin susceptible to attack by a nucleophilic group in the enzyme active site

(Enz-NUC, Figure 2) which leads to covalent binding of the substrate analog to the enzyme, blocking the approach of the true substrate (Path a). An alternative mechanism[46] could involve transimination (Path b) of the unsaturated amine-pyridoxal phosphate adduct by an active site amino group (Enz-NH_2, Figure 2) followed by nucleophilic attack of the product enamine on the electrophilic center of the PLP cofactor. The resulting modified pyridoxal phosphate complex may be tightly bound to the enzyme, giving irreversible inhibition.

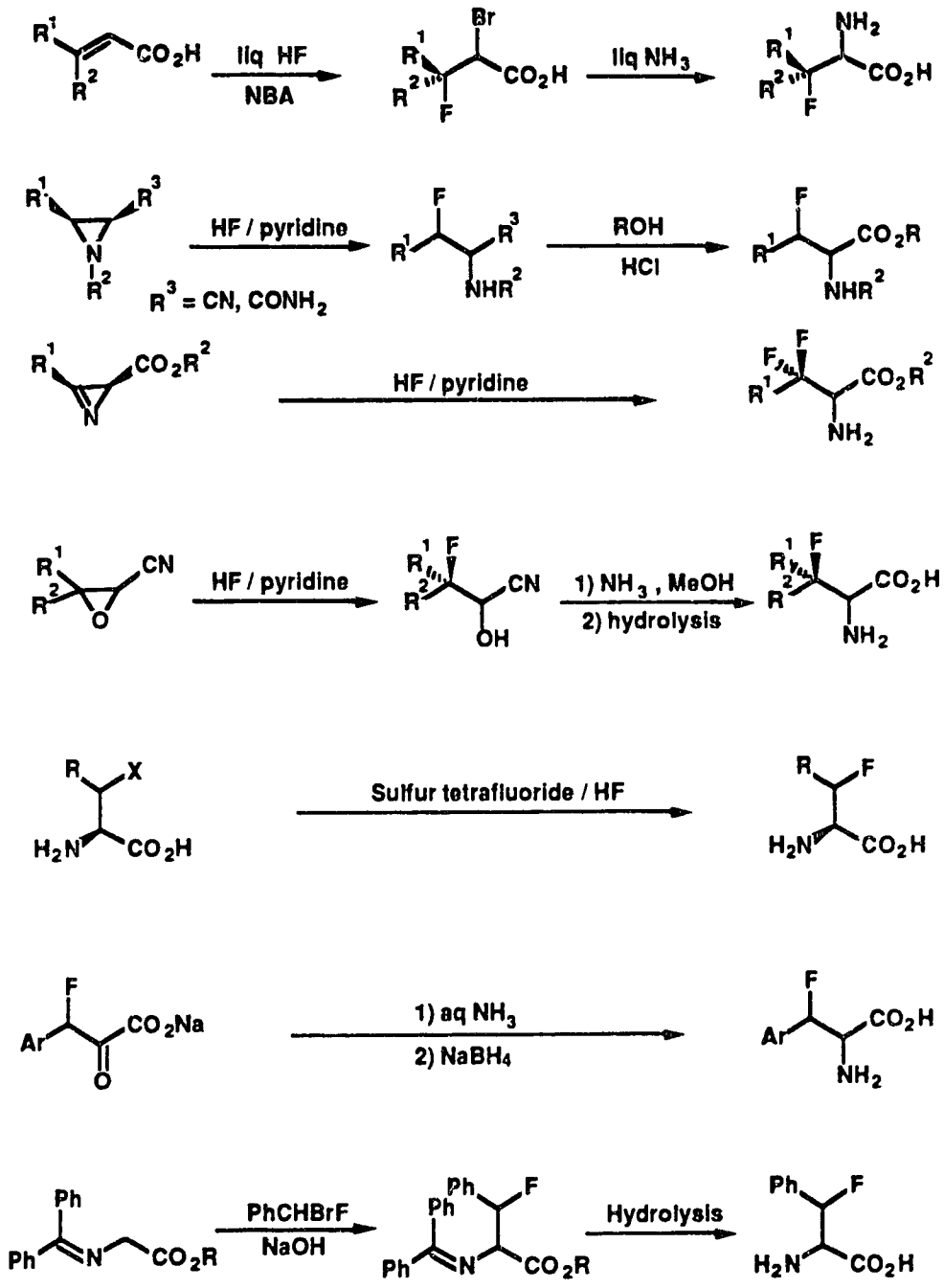
Although inhibition by α-fluoromethyl[52] and α-difluoromethyl analogues[51] has been systematically studied, investigation of other β-fluoro amino acids (with the exception of fluorinated alanine analogues) has yet to be reported, presumably due to the unavailability of selective synthetic methodology for the preparation of the "internally fluorinated" analogues. Previous studies[56] have indicated that in some cases, α-difluoromethyl analogues may not be useful due to the inability of such species to enter the enzyme active site. The synthesis of the β-fluoro analogues which should be true mimics of the substrate amino acids is of special interest in such situations. The significant biological activity of known β-fluoro amino acids and the potential for preparation of new analogues with chemotherapeutic potential make the synthesis of these molecules desirable.

The preparation of β-fluoro-α-amino acids has been of interest for a long time. Previous synthetic approaches (Figure 3) include the following: ammonolysis of 2-bromo-3-fluoro carboxylic acids,[30] reaction of azirines,[31,32] aziridines[33] or glycidonitriles [34,35] with hydrogen fluoride in pyridine; fluorodehydroxylation or desulfurization of β-hydroxy or β-thiol amino acids with sulfur tetrafluoride in liquid hydrogen fluoride,[36-38] reductive amination of fluoropyruvic acids,[39,40] and fluoroalkylation of glycinate anions.[41]

Although generally applicable, these procedures often require special precautions due to the toxicity of the reagents. Fluorodehydroxylation and fluorodesulfurisation, for example, require sulfur tetrafluoride which is extremely toxic. The fluoropyruvates used in

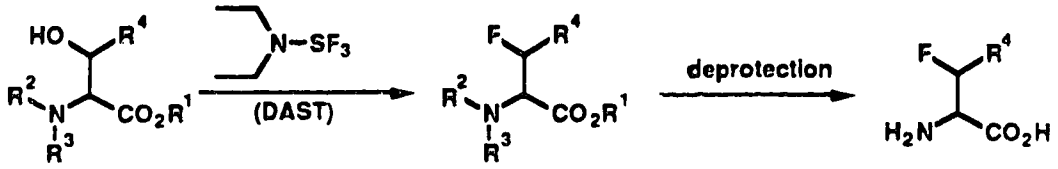
the reductive amination procedure are prepared by using elemental fluorine, and the HF/pyridine reagent, although easier to handle than liquid HF, usually requires special

Figure 3. Methodologies for the synthesis of β-fluoro α-amino acids.



reaction vessels. The present work describes the use of the mild fluorinating agent, (diethylamino)sulfur trifluoride (DAST)[57,58] for synthesis of aliphatic β-fluoro amino acids from the corresponding β-hydroxy amino acid derivatives (Figure 4).

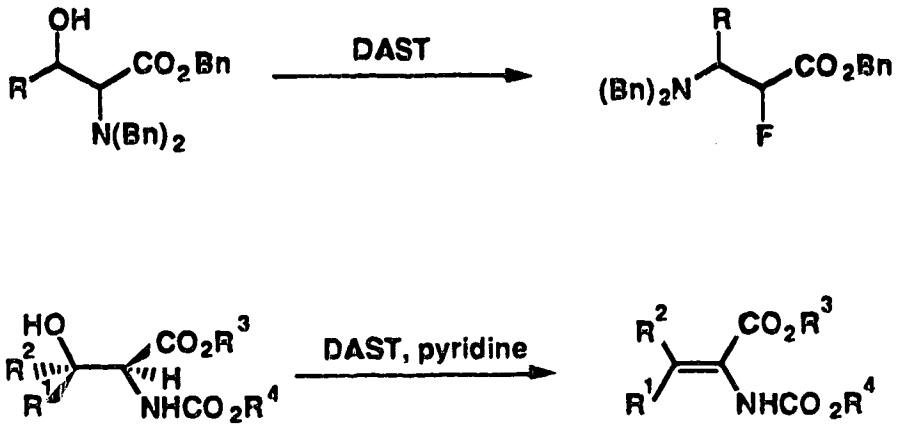
Figure 4. General approach to aliphatic β-fluoro α-amino acids using DAST as the fluorinating agent.



The above approach should not only avoid the use of toxic reagents but also provide access to a procedure that would, in principle, be limited only by the β-hydroxy amino acid derivatives used as starting materials. Since these should be easily available by simple aldol type condensation of a suitable protected glycine derivative and an aldehyde or a ketone, the present approach seems attractive.

As a mild reagent for substitution of hydroxyl groups by fluorine, DAST has been employed extensively in the synthesis of fluorinated carbohydrates[59-62] but has not been utilized on a general basis in the preparation of free β-fluoro-α-amino acids from corresponding β-hydroxy derivatives. In a single report[63] fluorodehydroxylation with DAST has been used in the preparation of β-fluorovaline methyl ester and fluorophenylalanine methyl ester from diketopiperazine (bis) lactim ether derivatives. However saponification of such methyl ester products frequently leads to decomposition with loss of fluoride.[39,41] Dehydration during the DAST reaction was also observed. Previous studies on the reaction of DAST with N-protected β-hydroxy amino acid esters have usually yielded[63] the corresponding dehydro compounds[64] or the rearranged α-fluoro-β-amino acids[65] (Figure 5).

Figure 5. Rearrangement and dehydration of β-hydroxy amino acid derivatives with DAST.

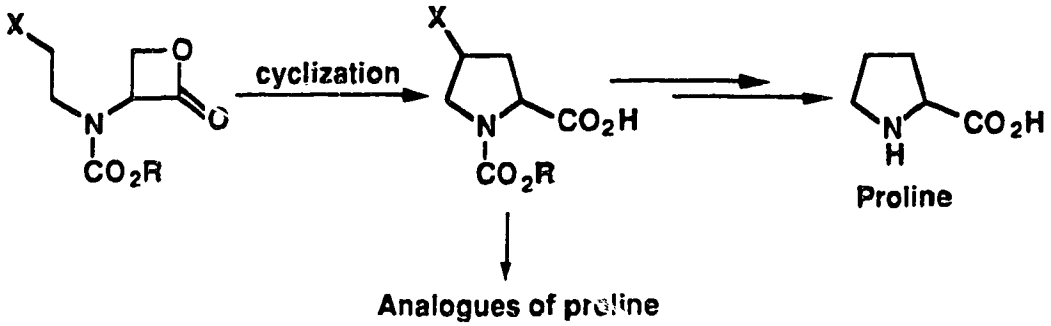


The present study describes successful conversions of β-hydroxy-α-amino acid derivatives to the corresponding β-fluoro derivatives using DAST as the fluorinating agent, and single step deprotection of these to the free β-fluoro-α-amino acids.[66]

As in the synthesis of β-fluoro-α-amino acids, β-hydroxy amino acid derivatives are versatile synthetic intermediates and may be used in one of several ways to modify the basic amino acid framework. One such application of a naturally occurring β-hydroxy amino acid, serine, has been its conversion to β-lactones which are useful intermediates in the synthesis of a variety of enantiomerically pure β-substituted α-amino acid derivatives.[67-70] In a variation of this approach, a potential synthesis of the amino acid proline (D or L) and its analogues was investigated. L-Proline is a component in a large variety of pharmaceutical products, for example angiotensin converting enzyme (ACE) inhibitors (e. g., Captopril[71] and Enalapril[72]). Analogues of proline are involved in a host of biological processes. Hydroxyproline for example is a constituent of collagen. Bicyclic hydantoins derived from L-proline are effective as fungicides.[73] Proline and its derivatives and chiral diamines that can be prepared from either L-proline or L-hydroxyproline in high optical purity are employed in asymmetric synthesis.[74-78] A great deal of effort has been

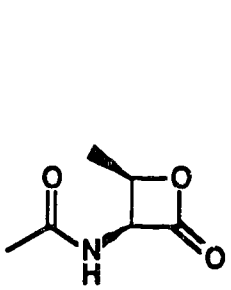
recently expended[79-85] to find stereospecific routes to proline and its analogues. Since L-proline is such an attractive synthetic target, a possible approach using intramolecular cyclization of N-modified-L-serine-β-lactone (Figure 6) to the requisite proline nucleus was investigated. The preparation of such β-lactones and the results of these cyclization studies are presented.

Figure 6. Approach to proline and analogues using N-modified serine β-lactones.

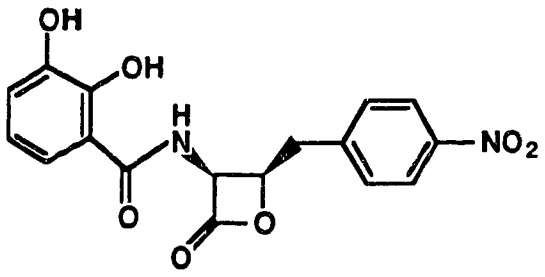


It is of interest to note that the N-protected α-amino-β-lactones, N-acetyl-L-threonine-β-lactone[86,87] and obafluorin[88,89] (Figure 7), are among the few naturally occuring β-lactones produced in microbes that exhibit antibiotic activity.

Figure 7. Naturally occuring β-lactone antibiotics.



N - Acetyl L - Threonine β - Lactone

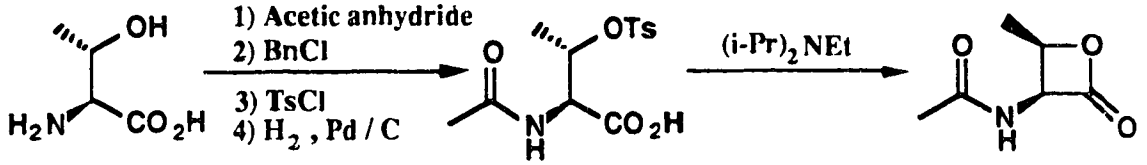


Obafluorin

The mechanism of action of these novel β-lactones may be similar to that of β-lactam antibiotics like penicillin. If a general synthesis of such β-substituted α-amino β-lactones were to become available, it would be possible to to study their structure-activity relationships and the mode of action.

Previous attempts[87] to synthesize N-acetyl-L-threonine-β-lactone have proceeded in very low yield. Direct cyclisation of N-acetylthreonine with dicyclohexylcarbodiimide (DCC) and 4-(N, N-dimethylamino)pyridine produced the coresponding lactone in only 0.8% estimated yield. An alternative method involving activation of the hydroxyl group in DL-*allo*-threonine gave N-acetyl-threonine β-lactone in 1.6% yield over five steps (Figure 8).

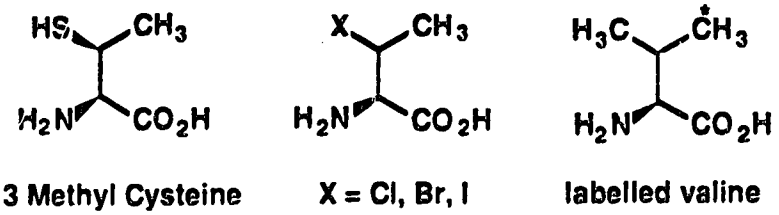
Figure 8. Synthesis of N-acetyl threonine β-lactone.



In addition to their biological activity, β-substituted-α-amino-β-lactones are of special interest as intermediates in the synthesis of novel amino acids. The enantioselective synthesis of both natural and unnatural amino acids has been the focus of many recent investigations.[13-29] Among the vast number of known amino acids,[1] β-disubstituted-α-amino acids constitute an interesting group due to the presence of two adjacent chiral centers in the molecule. Several β-methyl amino acids occur naturally[1] and are attractive synthetic targets. For example, 3-methyl-cysteine,[90-92] is a moiety of β-methyllanthionine, a constituent amino acid of the peptide antibiotic nisin. β-Halo-α-amino butyrates have been employed in several biological investigations and mechanistic studies of enzymatic

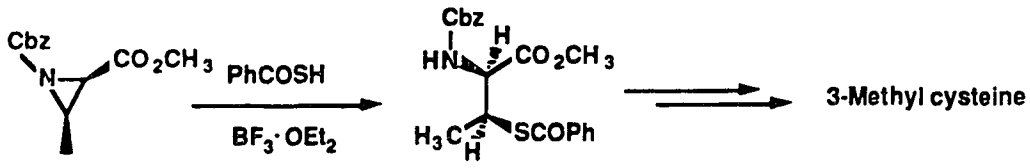
reactions.[93-101] Labelled valine[102,103] (Figure 9, label denoted by *) has been employed in studies on penicillin biosynthesis.[104]

Figure 9. Examples of β-disubstituted α-amino acids.



The chemical synthesis of these β-methyl amino acids (except labelled valine) has usually involved threonine as the starting material. For example, threo 3-methyl cysteine, has been synthesized[91] from a 2-aziridinecarboxylic acid derivative[91,105,106] (prepared by a six step procedure from D-threonine) by stereospecific ring opening with thiobenzoic acid (Figure 10).

Figure 10. Synthesis of 3-methyl cysteine

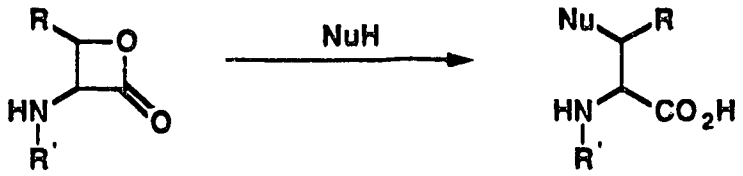


The above procedure, however has not been extended to synthesize other β-methyl amino acids with the exception of β-alkoxy-β-methyl amino acids which were prepared analogously. Stereospecifically labeled valine has been synthesized by a multi-step procedure[102,103] and enzymatic resolution is necessary to isolate pure enantiomers. In addition to the examples cited above, several other β-methyl amino acids occur naturally[1]

and the development of a general synthetic strategy for the preparation of these compounds seems desirable.

An attractive approach to the synthesis of β-methyl-α-amino acids and other β-disubstituted 2-amino acids involves regiospecific addition of a nucleophile at the β position of a β-lactone derived from threonine or other β-hydroxy amino acids[107-109] (Figure 11).

Figure 11. Synthesis of β-disubstituted α-amino acids by ring opening reactions of α-amino β-alkyl β-lactones.

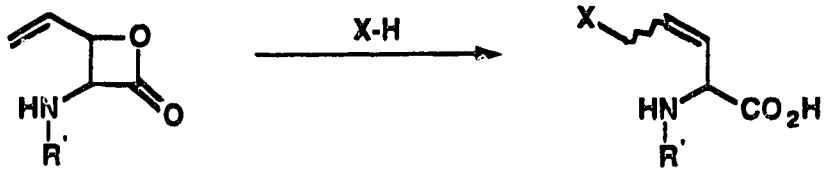


Such an approach would require minimal derivatization of the substrate amino acid and would also provide the product as a single stereoisomer, depending on the stereochemistry of the ring opening reaction. It should also be possible to vary substituents on the lactone (R, Figure 11), thereby providing access to a diversity of products. The utility of serine-β-lactones in the synthesis of stereochemically pure β-substituted alanine derivatives by a similar approach has been previously demonstrated.[67-69] In addition, stereochemically pure β-hydroxy α-amino acids (starting materials for β-lactones) are now readily available,[110-124] and both threonine and *allo*-threonine are commercially available as pure L- and D-isomers. Since β-lactones derived from 3-hydroxybutyric acid have been shown to react with nucleophiles selectively at the β position,[125,126] the above approach is very attractive.

Previous studies have indicated that β-vinyl- and β-ethynyl-β-propiolactones undergo S_N2' ring opening reactions with organocopper reagents[127,128] (Figure 12). Hence the approach may potentially be extended to the synthesis and ring opening reactions

of the β-vinyl-α-amino-β-lactone (R = CH_2CH, Figure 11). This would provide access to β, γ-unsaturated amino acids (Figure 12), some of which are natural products possessing antibiotic and enzyme inhibitory properties.[129-135]

Figure 12. Approach to β, γ-unsaturated α-amino acids from β-vinyl α-amino β-lactone.



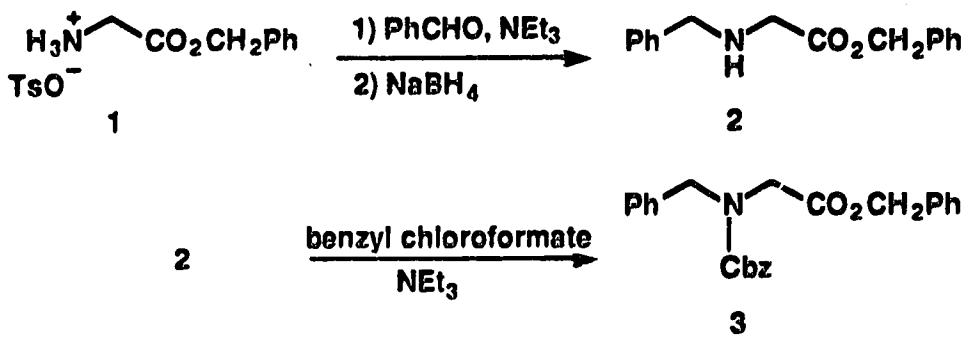
In the present work are described syntheses of optically pure N-protected β-lactones derived from L-threonine and related amino acids and studies on their ring opening reactions with several heteroatom and carbon nucleophiles.

Results and Discussion

Synthesis of β-Fluoro-α-Amino Acids

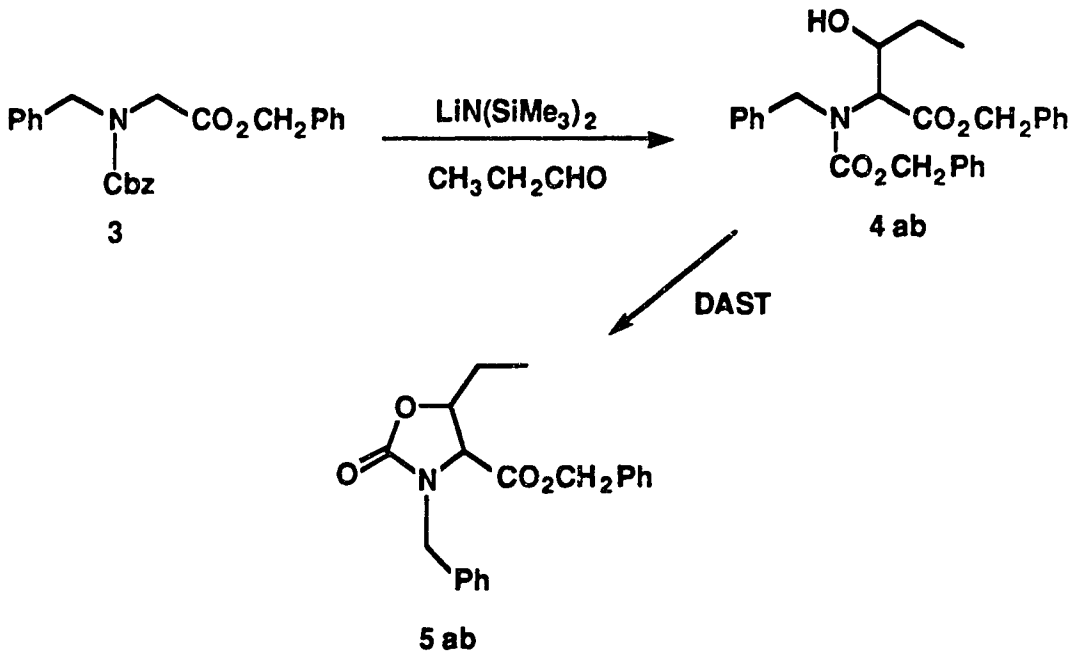
The reaction of alchohols and carbonyl compounds (aldehydes and ketones) with (diethylamino)sulfur trifluoride (DAST) to produce the corresponding mono- and difluorinated compounds is of a general type and especially attractive due to the mild reaction conditions.[57,58] Our approach to the synthesis of β-fluoro-α-amino acids using DAST as the fluorinating agent (Figure 4) required a synthesis of protected β-hydroxy amino acid derivatives which would serve as starting materials. These should be easily available by aldol-type condensation reactions of a suitably protected glycine derivative with a variety of aldehydes and ketones. Although the most direct synthesis would involve condensation[123,136] of an N-acyl glycine alkyl ester with a carbonyl compound, the resulting β-hydroxy amino acid derivative was thought to be unsuitable for fluorination with DAST due to possible side reactions involving the N-acyl group. Even if fluorination were successful, decomposition with loss of fluoride during saponification of the alkyl ester seemed likely.[39,41] Glycine esters protected as N, N-dialkyl derivatives were also ruled out since it is known that such species undergo intramolecular rearrangement[65] during the fluorination reaction (Figure 5). It was therefore necessary to use a glycine derivative that could be deprotected under conditions that would prevent undesirable side-reactions and also avoid loss of fluorine. Hence the readily available benzylglycinate p-toluenesulfonate salt[137] (**1**) was monoalkylated to give benzyl N-benzylglycinate (**2**) which was further converted to the fully protected benzyl N-benzyl-N-(benzyloxycarbonyl) glycinate (**3**) (Scheme 1). This is the starting material in the following aldol reactions.

Scheme 1.



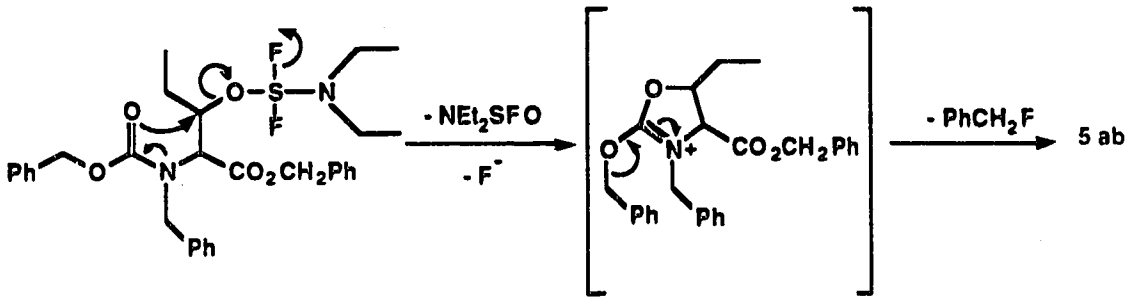
Generation of the enolate of **3** [$LiN(SiMe_3)_2$, THF, -78 °C] and condensation with propionaldehyde gives **4** as a mixture of diastereomers **4a** and **4b** in 62% yield. However reaction of this β-hydroxy amino acid ester with DAST[57,58] in dichloromethane at -78 °C gives only the oxazolidinone **5** as a diastereomeric mixture (**5a** and **5b**, 75% yield) (Scheme 2).

Scheme 2.



A plausible mechanism for oxazolidinone formation from **4** is given below (Figure 13).

Figure 13. Oxazolidinone formation from β-hydroxy amino acid derivatives.

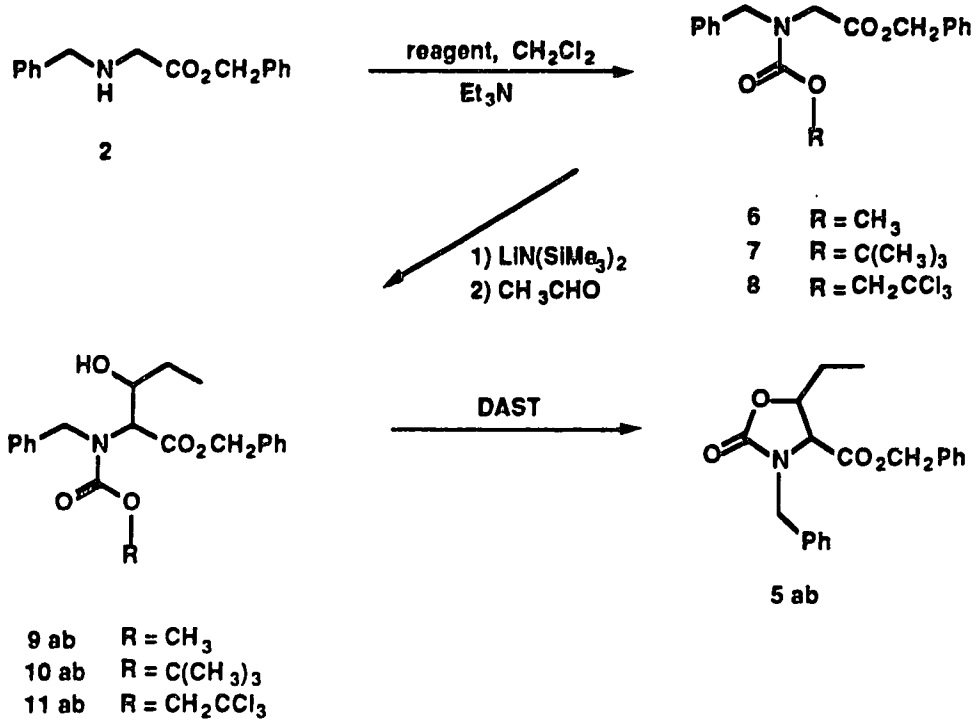


Initial activation of the hydroxyl group by DAST followed by rapid intramolecular attack of the carbamate oxygen on the activated β carbon and charge neutralization by loss of the benzyl group would give **5**. Since the latter step can in principle proceed by either S_N2 attack of fluoride on the benzylic carbon or by an S_N1 process involving a benzylic cation, it seemed that appropriate choice of an alkyl group in the carbamate could suppress either of these processes. It is of interest to note that N-(Cbz) β-hydroxy amino acid esters analogous to **4** have been shown[64] to undergo exclusive dehydration when treated with DAST in the presence of pyridine. The absence of a base and a very facile intramolecular reaction thus seem to favour oxazolidinone formation in the present case.

Variation of the alkyl group on the carbamate was investigated next. Treatment of **2** with methyl chloroformate, *tert*-butyl pyrocarbonate and trichloroethyl chloroformate gives the methyl carbamate **6**, tert-butyl carbamate **7**, and trichloroethyl carbamate **8** derivatives respectively (Scheme 3). These structural modifications have no significant effect on the aldol reaction, and the corresponding aldol products **9ab**, **10ab**, and **11ab** can be readily obtained (62%, 55%, and 46% yield) from **6**, **7**, and **8**, respectively using the same

conditions [$LiN(SiMe_3)_2$, THF, -78 °C] as for **4ab**. Unfortunately the reaction of each of these β-hydroxy amino acid esters with DAST in dichloromethane at -78 °C again produces **5ab** in yields of 54-91% rather than the desired β-fluoro products (Scheme 3).

Scheme 3.

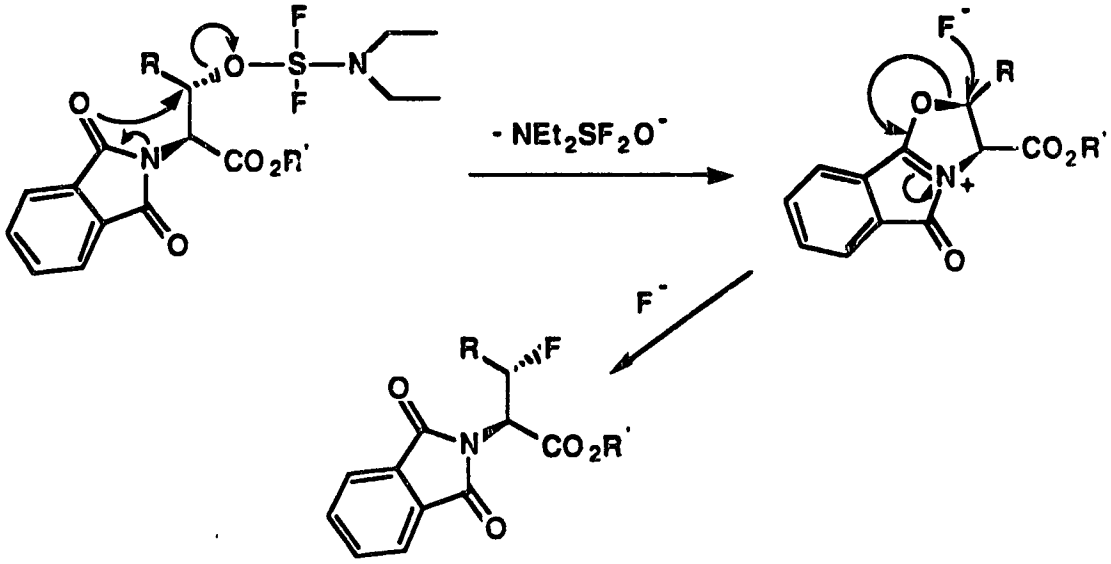


These results show that intramolecular cyclization is still the predominant reaction and the loss of the carbamate alkyl group can proceed by different mechanisms depending on its structure (i.e. S_N1 for **10** and S_N2 for **9**). It is thus evident that a carbamate protecting group would be of little use for successful fluorination; a change of the protecting group on nitrogen is therefore necessary.

Use of an N-phthaloyl protecting group potentially could prevent *subsequent breakdown* of the nitrogen protecting group after intramolecular participation. The approach is also interesting because neighbouring group participation by the phthalimido group[138] in

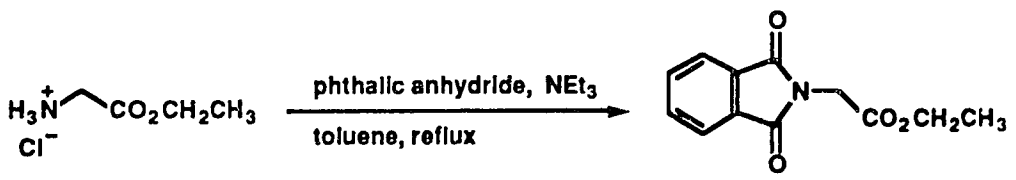
the fluorination step could lead to a stereospecific substitution by fluoride ion. The stereochemistry of the starting alcohol would then fix the stereochemistry of the fluorination step as retention of configuration (Figure 14).

Figure 14. Possible neighbouring-group participation by the phthalimido group in the fluorination of β-hydroxy amino acid derivatives.



For initial studies the requisite ethyl N-(phthaloyl)glycinate (**12**) was prepared from the commercially available ethyl glycinate hydrochloride by modification of the literature procedure[139] (Scheme 4).

Scheme 4.

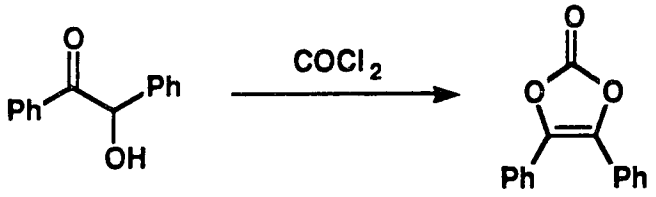


12

Although methyl N-(phthaloyl)glycinate[139] undergoes formylation in the presence of a base and a formate ester,[140,41] attempted condensation of **12** with propionaldehyde in the presence of a base [$LiN(SiMe_3)_2$ or potassium *tert*-butoxide] at low temperature (-78 °C) leads to a complex reaction and no β-hydroxy amino acid derivative could be isolated. Presumably the phthalimido group acts as an acylating agent and self condensation may be a competing reaction.

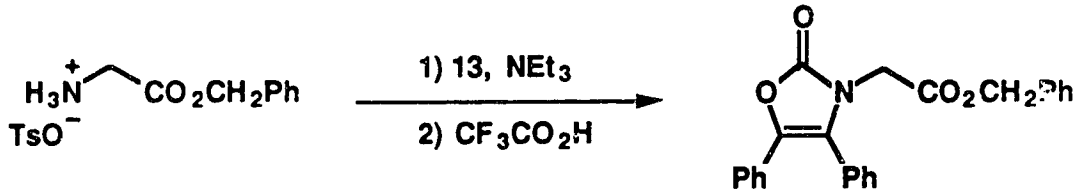
Since a cyclic protecting group was still thought to be necessary to prevent oxazolidinone formation in the fluorination step, the nitrogen was protected as a 4, 5-diphenyl-4-oxazolin-2-one moiety, a protecting group which had been reported to be stable to acidic or basic conditions but readily cleaved by hydrogenolysis[142]. Benzyl glycinate p-toluenesulfonate salt[137] (**1**) was treated with 4,5-diphenyl-1,3-dioxol-2-one[142] (**13**) (prepared from benzoin and phosgene by the literature procedure[142]) (Scheme 5) by a modification of the literature procedure[142] to give the required protected glycine derivative benzyl 2-(4, 5-diphenyl-2-oxo-4-oxazolin-3-yl) ethanoate (**14**) in 81% yield (Scheme 6).

Scheme 5.



13

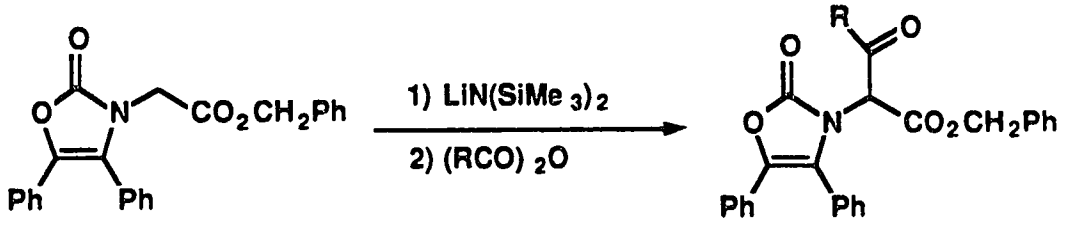
Scheme 6.



1 **14**

At this stage it appeared that β, β-difluoro-α-amino acid derivatives could also be prepared from **14**. Hence **14** was acylated with acetic anhydride (LDA, TMEDA, -78 °C) to furnish **15** in 21% yield. Several modifications involving acetyl chloride as the acylating agent, and $LiN(SiMe_3)_2$ as the base did not affect the yield significantly. Acylations with propionic and butyric anhydride furnished **16** and **17** in 28% and 31% yield respectively (Scheme 7). Although compounds **15** and **16** are stable, compound**17** is light sensitive. The reason for this anomalous behaviour is not known at present.

Scheme 7.

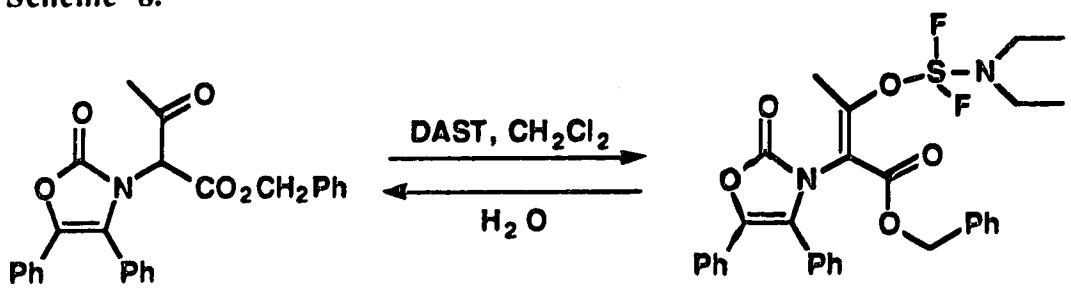


14

15 R = CH_3
16 R = CH_2CH_3
17 R = $(CH_2)_2CH_3$

Despite the low yields for the acylation reaction, the reaction of **15** with DAST was investigated. Surprisingly, no reaction was observed under a variety of conditions (-78 °C to +20 °C, 6 h; 0 °C to 20 °C, 6 h; or 20 °C overnight). The lack of reactivity of **15** may be attributed to enolization of the β-keto ester functionality followed by reaction with DAST to produce an intermediate fluorosulfurane which does not react further. Hydrolysis upon addition of water, to quench the reaction, produces **15** (Scheme 8).

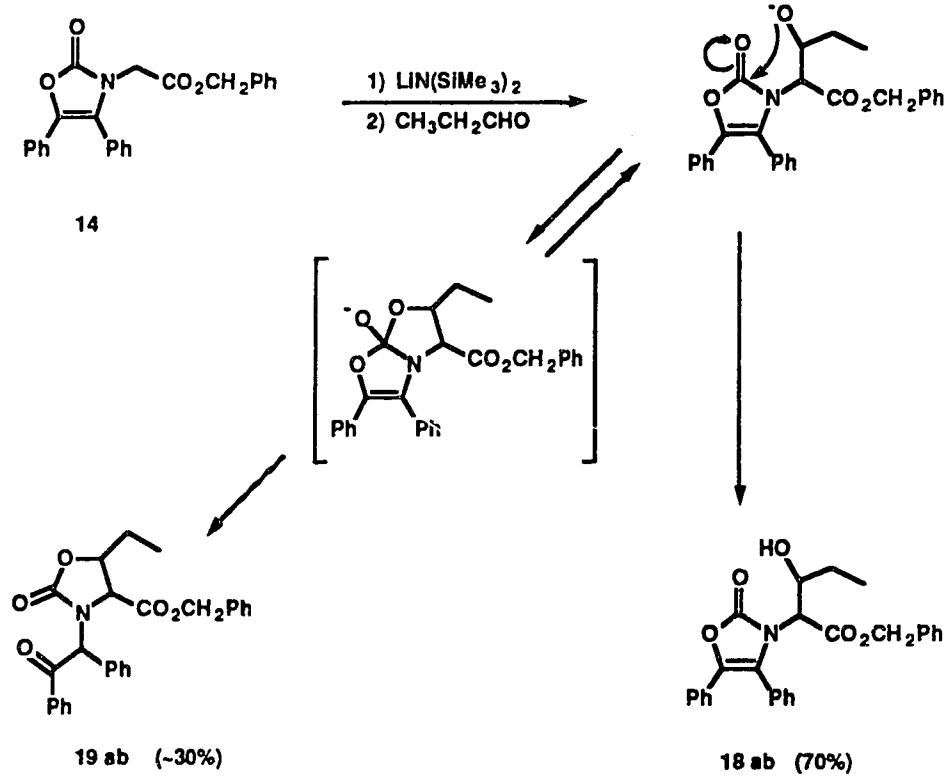
Scheme 8.



15

The above approach was therefore not pursued and aldol reactions of **14** were investigated. Condensation of **14** with propionaldehyde, using $LiN(SiMe_3)_2$ in THF at -78 ^oC gives the expected product **18** (~70%) and by-product **19** (~30%), each as a mixture of diastereomers (**a**: major; **b**: minor, Scheme 9).

Scheme 9.



14

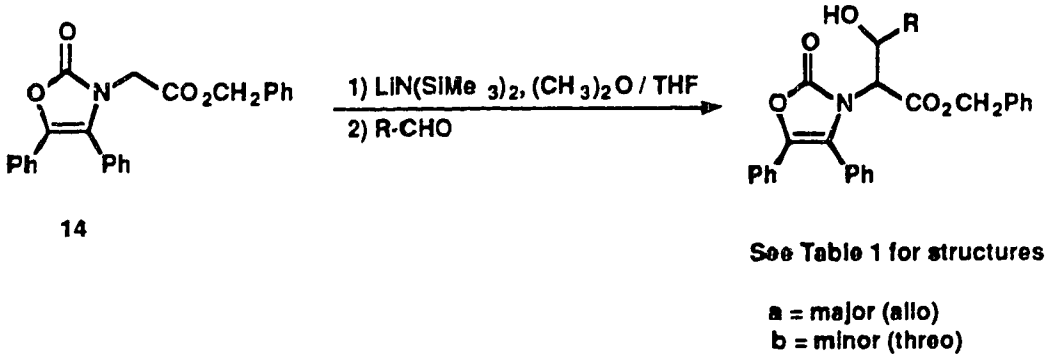
19 ab (~30%)

18 ab (70%)

The oxazolidinone **19ab** arises from intramolecular reaction of the initially formed β-alkoxide with the carbonyl of the oxazolinone protecting group and subsequent ring opening (Scheme 9). Although change in the reaction quench conditions (H_2O, HCl or AcOH) at low temperature did not significantly alter the amount of **19**, warming the reaction mixture to room temperature before quenching gave exclusively **19** and no **18**. This suggested that attack of the β-alkoxide was temperature dependant and lower temperatures should favour **18**. Indeed, when the reaction was done at -130 °C in dimethyl ether/THF, the yield of **18** rose to 84% and no **19** could be detected. An analogous temperature dependant intramolecular acyl transfer reaction has recently been observed[114] in the condensation of 1-benzoyl-3-methyl-imidazolidin-4-one derived enolates with aldehydes.

These conditions ($LiN(SiMe_3)_2$, -130 °C) are generally applicable to the reaction of **14** with a variety of aldehydes to form the β-hydroxy compounds. Thus reaction of **14** with acetaldehyde, butyraldehyde, isovaleraldehyde, isobutyraldehyde, and benzaldehyde gives **20ab**, **21ab**, **22ab**, **23ab** and **24ab** respectively as diastereomeric mixtures (Scheme 10) (Table 1).

Scheme 10.



14

See Table 1 for structures

a = major (allo)
b = minor (threo)

Table 1: Condensation of benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl) ethanoate (14) with non-functionalized aldehydes.

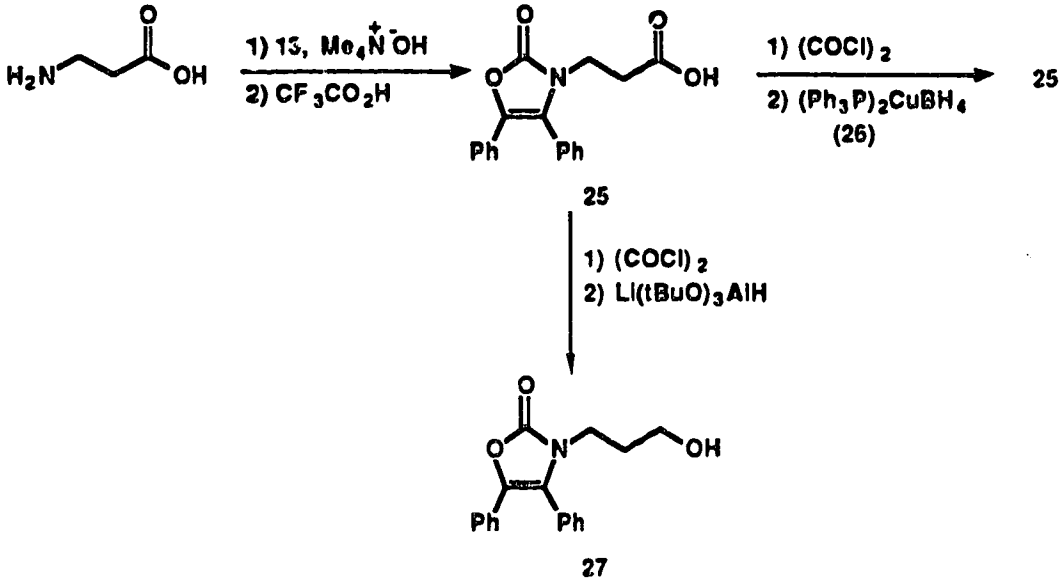
Compound No.[a]	R'	Temp (°C)	Time (h)	Yield, % [b]
18	Et	-130	1.5	84
20	Me	-130	4.0	90
21	nPr	-130	4.0	80
22	iBu	-130	4.0	70
23	iPr	-130	3.0	81
24	Ph	-130	1.5	79

[a]Each compound exists as a mixture of two diastereomers; **a** is major, **b** is minor. [b]Isolated yield for mixture of diastereomers.

The preparation of β-fluoroornithine and β-fluorolysine is of interest since these analogues may have interesting biological properties. β-Fluoroasparagine[50] has antileukemic activity and is an attractive synthetic target. The synthesis of the corresponding β-hydroxy derivatives, that may be fluorinated with DAST, required the synthesis of functionalized aldehydes.These were prepared in a few steps from readily available starting materials. Commercially available β-alanine was considered suitable for the synthesis of a 3-carbon amino aldehyde that would give a β-hydroxyornithine derivative by aldol condensation with **14**. Treatment of β-alanine with **13** by modification of the literature procedure[142] gave the protected amino acid **25** in 82% yield. Conversion of **25** to the acid chloride followed by reaction with bis(triphenylphosphine)copper (I) tetrahydroborate[143] (**26**) gave only the starting acid after workup. Reduction of the acid

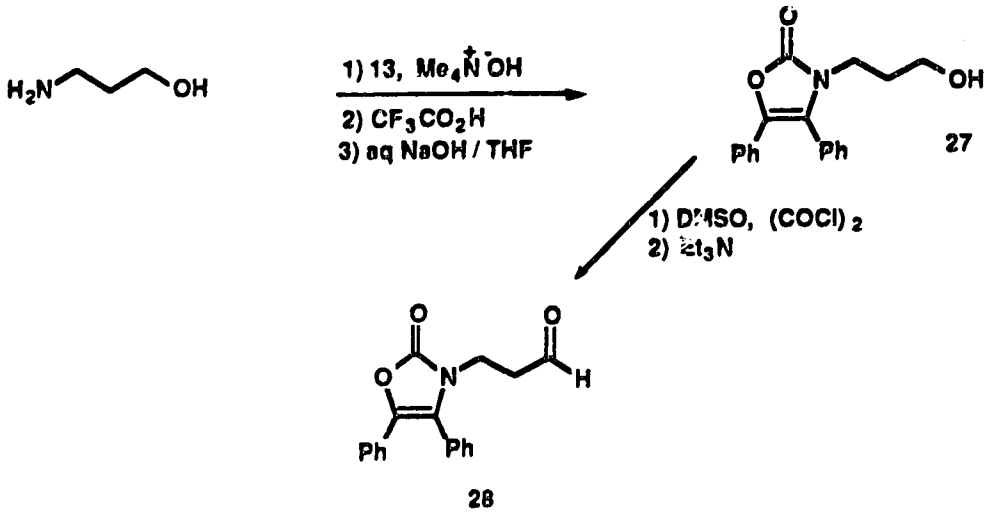
chloride with lithium tri-*tert* butoxyaluminohydride[144] gave the corresponding alchohol **27** in very low yield, the acid being recovered as the major product (Scheme 11).

Scheme 11.



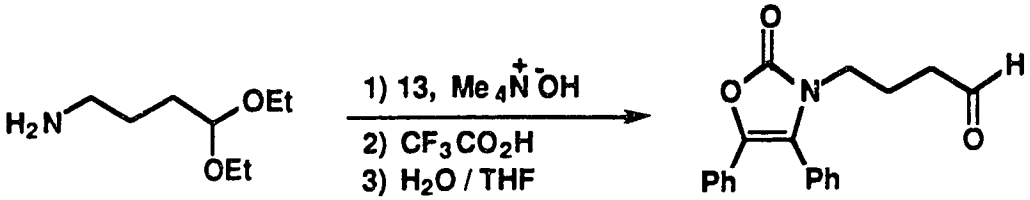
An alternative approach involving oxidation of alchohol **27** to the aldehyde **28** was successful. Alcohol **27** is readily prepared from 3-aminopropanol by reaction with **13** using a modification of the literature procedure[142] for protection of the amino group. Treatment with trifluoroacetic acid in the protection step produces the trifluoroacetate ester of **27**. This was hydrolysed to **27** (70% yield) with aqueous NaOH/THF. Swern oxidation[145] of **27** gives the N-protected 3-amino propionaldehyde derivative **28** in 89% yield (Scheme 12). This was used in the condensation reaction with **14** (see below).

Scheme 12.



The next goal was the preparation of a 4-carbon amino aldehyde. This would yield a β-hydroxylysine derivative upon condensation with **14**. Commercially available 4-aminobutyraldehyde diethylacetal is readily derivatized to the N-protected acetal as before. Removal of the acetal with aqueous trifluoroacetic acid gives the N-protected 4-aminobutyraldehyde derivative **29** in 65% yield (Scheme 13).

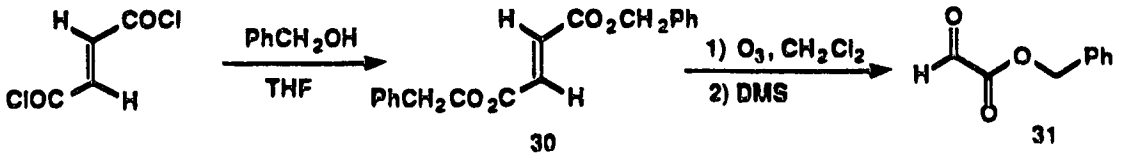
Scheme 13.



The preparation of an aldehyde leading to a β-hydroxy aspartic acid derivative was investigated next. Dibenzyl fumarate[146,147] (**30**), readily prepared in 88% yield by

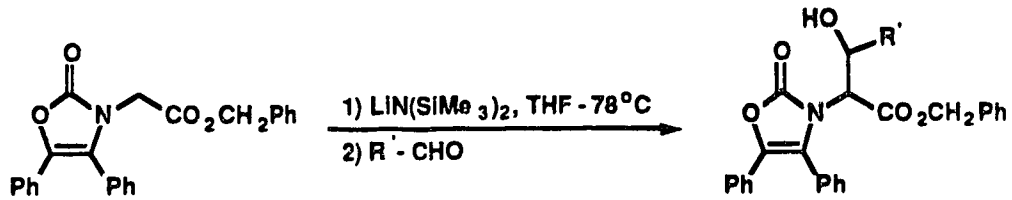
reaction of fumaryl chloride with benzyl alchohol, was ozonolysed to benzyl glyoxalate (**31**) using the literature procedure[148] (Scheme 14).

Scheme 14.



Condensation of aldehydes **28**, **29** and **31** with **14** [$LiN(SiMe_3)_2$, THF] gives the β-hydroxy derivatives **32ab**, **33ab**, and **34ab** as diastereomeric mixtures (Scheme 15). In such cases the reaction works better at higher temperature (-78 °C). Interestingly, competing oxazolidinone formation was not observed in these reactions and unreacted starting materials were always recovered. These results are summarized in Table 2.

Scheme 15.



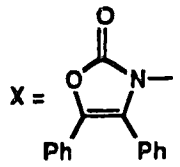
14

see Table 2 for structures

a = major (allo)
b = minor (threo)

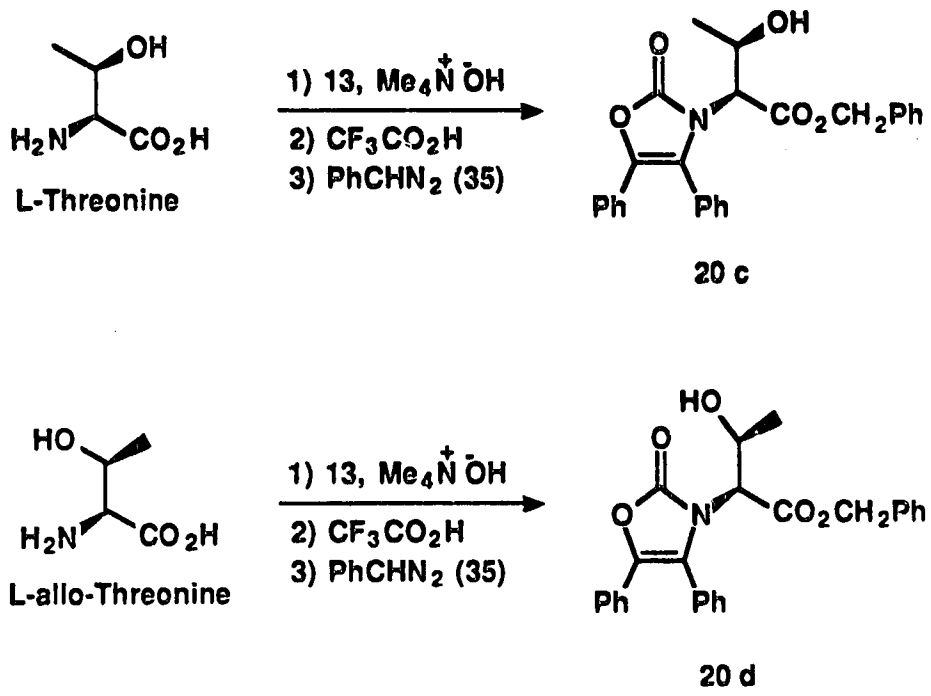
Table 2: Condensation of benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl) ethanoate with functionalized aldehydes.

Compound No.	R'	Temp. (°C)	Time (h)	Yield, %
32	CH_2CH_2X	-78	3	60
33	$CH_2CH_2CH_2X$	-78	4	55
34	CO_2CH_2Ph	-78	3	61

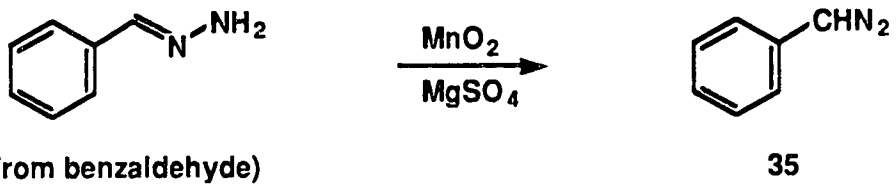


The aldol reaction shows a preference for the formation of one diastereomer of the β-hydroxy amino acid derivative over the other. To determine the relative stereochemistry of the major and minor diastereomers obtained in the aldol reaction of **14**, L-threonine (2S, 3R) and L-*allo*-threonine (2S, 3*S*) were independently converted to their 4, 5 diphenyl-2-oxo-4-oxazolin-3-yl benzyl esters **20c** and **20d**, respectively (Scheme 16). Reaction of L-threonine and L-*allo*-threonine with **13**, by modification of the literature procedure[142] for protection of the amino group, gives the corresponding N-protected amino acids. These were directly transformed to their benzyl esters **20c** (25% yield) and **20d** (35% yield) respectively by treatment with phenyldiazomethane[149,150] **(35)** (Scheme 17).

Scheme 16.



Scheme 17.

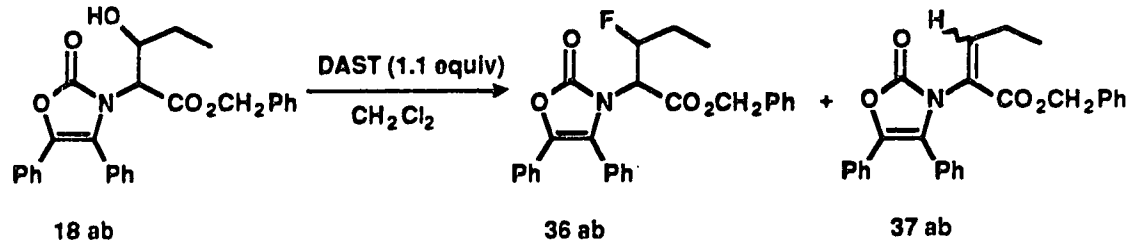


Examination of ^{1}H NMR spectra of **20c** and **20d** reveals that the C-2 hydrogen of the threonine derivative **20c** appears at δ 4.04 while that of the *allo*-threonine derivative **20d** occurs at δ 3.88, thereby showing that the major diastereomer **20a** obtained by condensation of **14** with acetaldehyde possesses the *allo*-threonine relative stereochemistry. The diastereomeric ratios (major:minor) are approximately 5:1. All β-hydroxy derivatives,

except **23** showed similar behaviour (δ C-2H allo < δ C-2H threo) and diastereomeric ratios.[151] The reason for the anomalous behaviour of **23** is not known at present.

With the requisite β-hydroxy amino acid derivatives available, their fluorodehydroxylation with DAST could be examined under a variety of conditions. Treatment of a solution of **18** (5:1 diastereomeric mixture) with DAST (1.1 eq, CH_2Cl_2, -78 °C to 20 °C) followed by aqueous workup provides the desired β-fluoro compound in ~50% yield as a 1:1 mixture of diastereomers **36a** and **36b**, along with 17% of the elimination product **37a** and **37b** also as a diastereomeric mixture (Scheme 18).

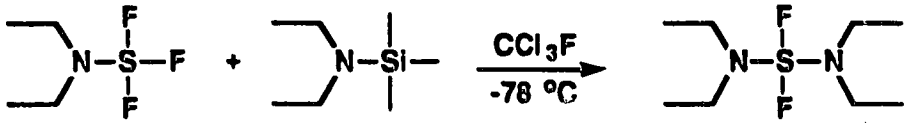
Scheme 18.



18 ab **36 ab** **37 ab**

All attempts to improve the yield of fluorination and reduce elimination using a variety of conditions failed. Since it was reported[58] that bis(dialkylamino)sulfur difluorides, are less reactive than the corresponding trifluorides like DAST and cause less rearrangement and elimination, fluorination of **18** with bis(diethylamino)sulfur difluoride (**38**) was attempted. Compound **38** was synthesized from DAST and diethylaminotrimethylsilane[152] by adaptation of the literature procedure[58] (Scheme 19).

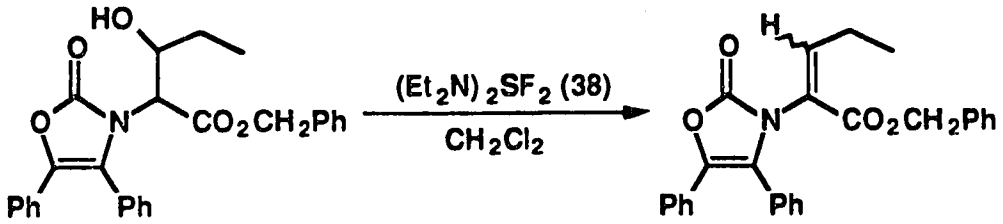
Scheme 19.



38

Treatment of **18** with **38**, unfortunately leads to exclusive elimination and no fluorination is observed. Compound **37** was isolated in 80% yield as a mixture of diastereomers (**a** and **b**) (Scheme 20).

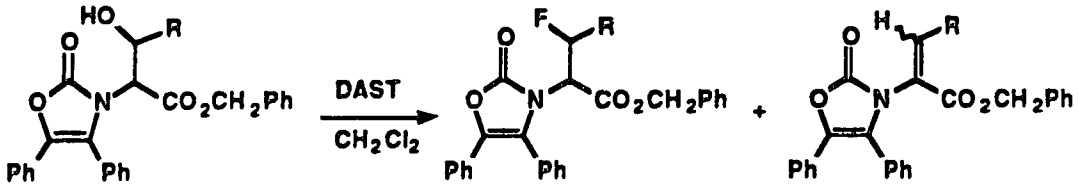
Scheme 20.



18 ab **37 ab (80%)**

Fluorination with DAST of the less functionalized β-hydroxy derivatives **20**, **21** and **22** affords the corresponding β-fluoro compounds **39ab**, **41ab** and **43ab** (45-65% yield) as nearly equal mixtures of diastereomers. In all these cases elimination is a side reaction, compounds **40ab**, **42ab**, and **44ab** are obtained as diastereomeric mixtures (12-24% yield) (Scheme 21). The yields of these reactions are summarized in Table 3 (see below).

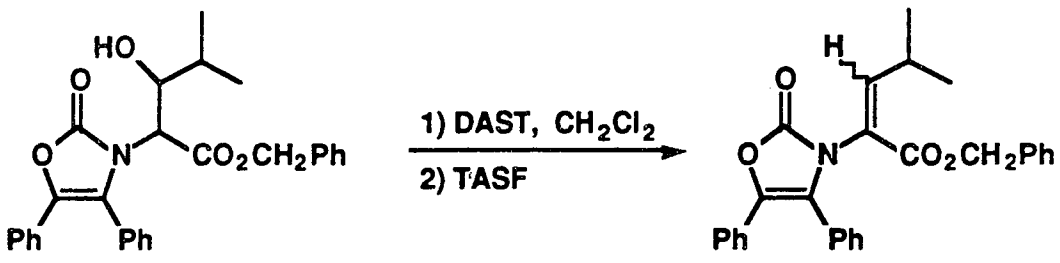
Scheme 21.



20 ab	**R = Me**	**39 ab**	**R = Me**	**40 ab**	**R = Me**
21 ab	**R = nPr**	**41 ab**	**R = nPr**	**42 ab**	**R = nPr**
22 ab	**R = IBu**	**43 ab**	**R = IBu**	**44 ab**	**R = IBu**

Treatment of compound **23** with DAST gives complex mixtures and no fluorination is observed. Since the desired fluorination requires attack by fluoride ion at the β carbon, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[153-155] (a good source of fluoride ion) was added at -78 °C after addition of DAST to **23**. Unfortunately this only increases the yield of elimination product **45** to 54% (Scheme 22, diastereomeric mixture), presumably because fluoride can act as a base to remove the α-hydrogen.[156] Steric hindrance by the isopropyl group may be favouring elimination over substitution in this case.

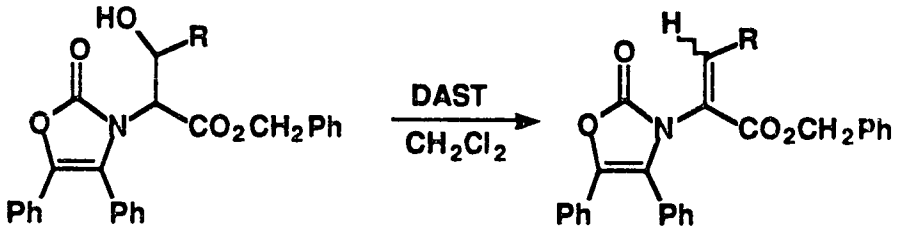
Scheme 22.



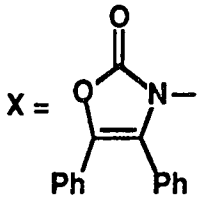
23 ab **45 ab**

Attempted fluorination of the functionalised β-hydroxy derivatives **32**, **33**, **34** with DAST was unsuccessful and dehydration products **46ab**, **47ab** and **48ab**, respectively, were obtained as diastereomeric mixtures (Scheme 23, c.f. Table 3). In each case an approximately 5:1 diastereomeric mixture of β-hydroxy derivatives is converted to a diastereomeric mixture of elimination products in a ratio other than 5:1.

Scheme 23.



32 ab	R = CH_2CH_2X	**46 ab**	R = CH_2CH_2X
33 ab	R = $(CH_2)_3X$	**47 ab**	R = $(CH_2)_3X$
34 ab	R = CO_2CH_2Ph	**48 ab**	R = CO_2CH_2Ph



Attempts to reduce carbocationic character at the β-carbon by decreasing the solvent polarity had no effect. Thus reaction of **32** with DAST in $CFCl_3$ gives only **46** in a yield comparable to that for the reaction in CH_2Cl_2 (~45% based on recovered starting material). The results of the fluorination/dehydration reaction with DAST are summarized in Table 3.

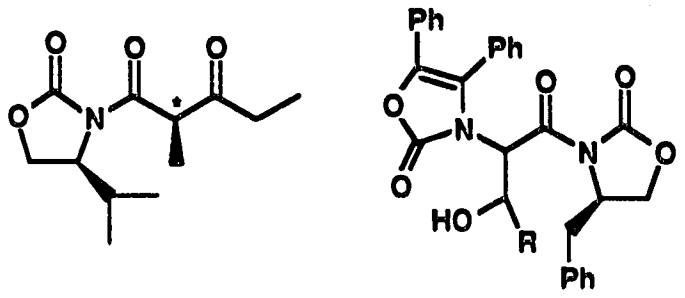
Table 3: Fluorination/dehydration reactions of β-hydroxy amino acid derivatives with DAST. (See Schemes 18-23).

Starting material	Fluorinated product	Dehydrated product	Yields, % Fluorination	Dehydration
18	**36**	**37**	48	17, (80)[a]
20	**39**	**40**	45	24
21	**41**	**42**	65	14
22	**43**	**44**	64	12
23		**45**		75[b]
32		**46**		46[c]
33		**47**		73[c]
34		**48**		76[d]

[a]Yield for reaction with $(Et_2N)_2SF_2$. [b]Reaction with DAST in the presence of excess TASF. [c]Yields based on recovered starting material. [d]Reaction of DAST only with major diastereomer.

Proton NMR spectra allow determination of the isomeric ratios of the products of the elimination reactions. By analogy to N-protected dehydro amino acids studied previously,[70,157-159] in which the vinylic proton is known to appear downfield in the *(Z)* isomer as compared to the *(E)* isomer, the major diastereomer in the isomeric mixture of elimination products (Table 3) was assigned the *(Z)* stereochemistry.

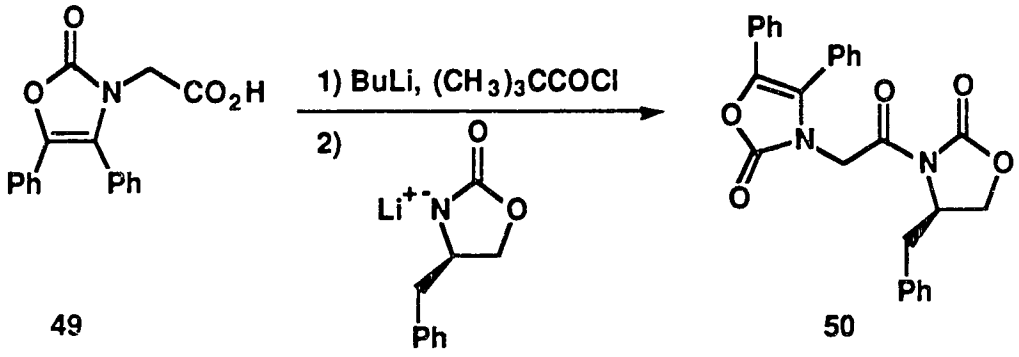
Since elimination could not be suppressed by modification of reaction conditions, an alternative approach was investigated. It has been observed[160] that β dicarbonyl compounds of the type **A** are resistant to enolisation at the chiral center (denoted by *).



A B

Hence it appeared that a β-hydroxy amino acid derivative of the type **B** would be less susceptible to dehydration due to steric constraints similar to those responsible for maintaining the stereochemical integrity at the enolisable chiral center in **A**. With this in mind, reaction of glycine with compound **13** affords **49** in 66% yield. Conversion of **49** to its mixed anhydride with pivaloyl chloride followed by reaction with the lithium salt of commercially available (*R*)-(+)-4-benzyl-2-oxazolidinone produces the requisite protected glycine derivative **50** (Scheme 24).

Scheme 24.

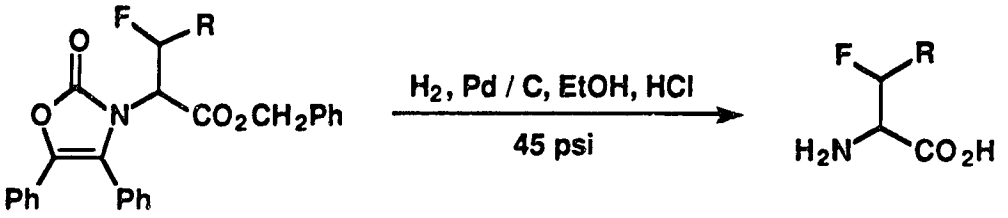


49 50

However, attempted condensation of the enolate of **50** with propionaldehyde as the electrophile fails, presumably due to inaccessibility of the α-position for steric reasons.[161] The approach was therefore not pursued.

Deprotection of the β-fluoro derivatives proceeds readily in high yield (88-99%) by hydrogenolysis. Thus **36ab** on hydrogenolysis (Pd/C, EtOH, HCl) affords β-fluoronorvaline[30] (**51**) as a nearly equal mixture of diastereomers in 88% yield without any cleavage of the carbon fluorine bond. This sequence is easily applied to the other β-fluoro derivatives **39**, **41**, and **43** to give the corresponding free β-fluoro amino acids **52ab**, **53ab**, and **54ab**, respectively, as a nearly equal mixture of diastereomers as determined by ^{19}F NMR spectroscopy (Scheme 25). These results are summarized in Table 4.

Scheme 25.



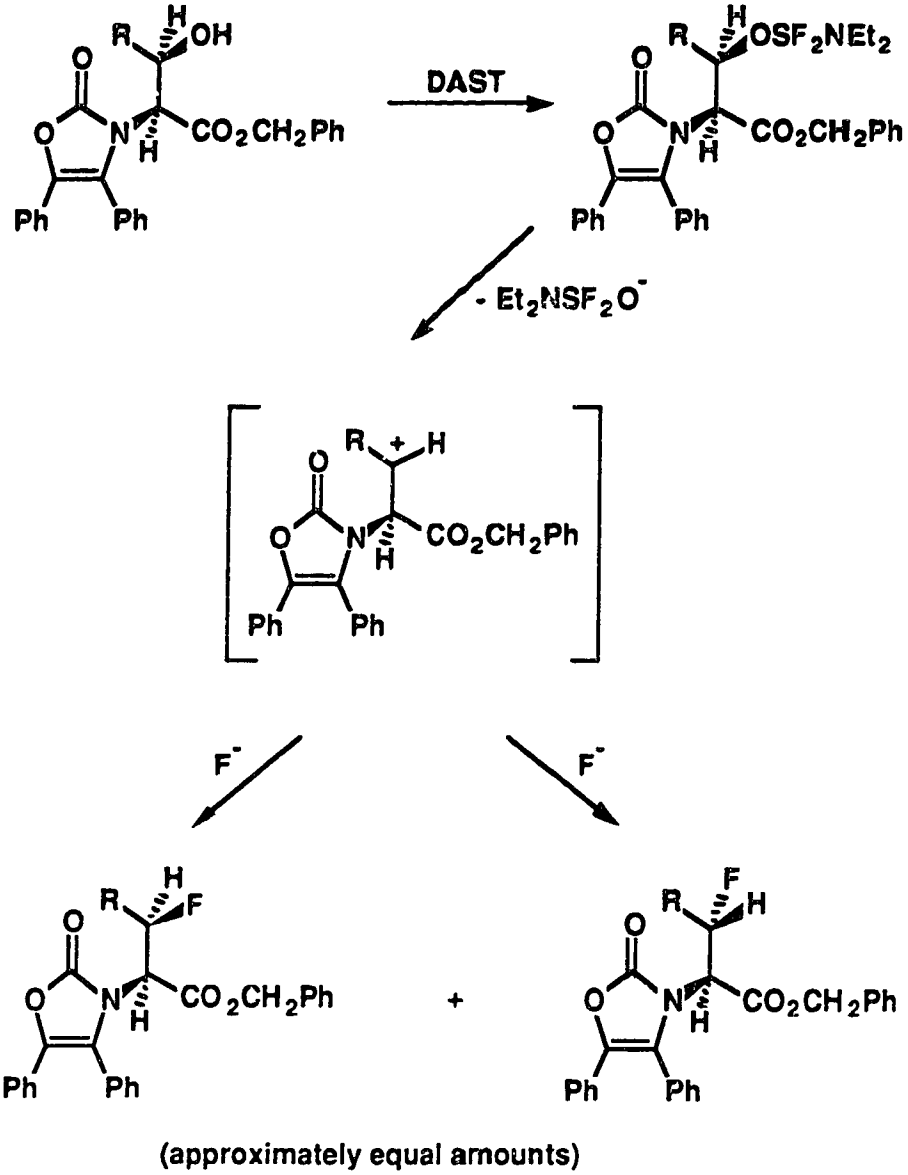
36 ab	R = Et	51 ab	R = Et
39 ab	R = Me	52 ab	R = Me
41 ab	R = nPr	53 ab	R = nPr
43 ab	R = iBu	54 ab	R = iBu

Table 4: Deprotection of β-fluoro-α-amino acid derivatives to β-fluoro-α-amino acids.

Starting material	Product	Yield, %
36	**51**	88
39	**52**	99
41	**53**	89
43	**54**	91

The conversion of an approximately 5:1 diastereomeric mixture of β-hydroxy derivatives to a approximately 1:1 diastereomeric mixture of β-fluoro compounds suggests that the fluorination reaction proceeds by a S_N1-type mechanism involving a carbonium ion which is attacked by fluoride ion to produce a 1:1 mixture of diastereomeric β-fluoro derivatives. The sequence of steps for a single diastereomer of the β-hydroxy derivative is shown (Scheme 26). The observed[58] rearrangement of isobutyl alcohol to produce *tert*-butyl fluoride upon treatment with DAST lends support to the above hypothesis.

Scheme 26.



Although several other reagents and methods are available[162-170] for the fluorination of organic compounds, they usually target fairly robust molecules (eg. hydrocarbons, steroids, aromatic compounds). The method developed for the synthesis of chemically sensitive β-fluoro amino acids using DAST as the fluorinating agent is therefore very useful. Although conversion of the β-hydroxy amino acid derivatives to the corresponding fluoro compounds is limited to cases having unfunctionalised side chains, the free β-fluoro α-amino acids are available in high yield (>88%) by single step hydrogenolytic deprotection. Previous investigations have indicated that deprotection of amino acid derivatives having β-fluoro on the parent side chain is usually problematic.[39,41] The present method offers an attractive alternative.

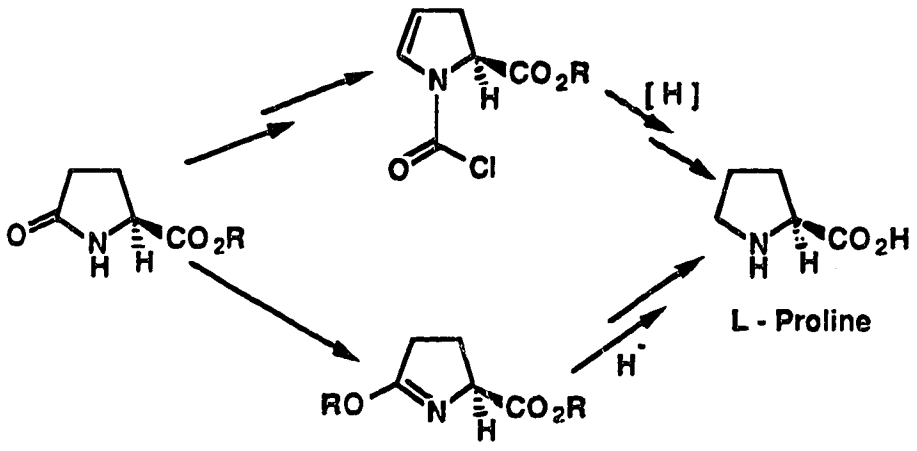
During the completion of this work a route to β-fluoro-α-amino acids from fluorinated amino carbohydrates was proposed.[171] The actual conversion of the functionalised carbohydrates to the amino acids has not yet been reported.

Synthetic Approach to Proline and Analogues using N-Modified L-Serine β-Lactones.

The amino acid L-proline is a proteinogenic amino acid that has gained importance as a central component in pharmaceutical products, agricultural chemicals, and asymmetric organic synthesis.[71-78] As a result, considerable effort has been devoted to the synthesis of L-proline in both racemic and optically pure form. Racemic proline[172] has been synthesized, for example, from pyrrolidinone,[173] pyrrolidine,[174] acrolein, HCN and ammonia,[175] and by reaction of acrolein with a protected 2-amino malonate.[176] Optically pure L-proline has been prepared from L-pyroglutamic acid using several approaches including reduction of the amide carbonyl in L-pyroglutamic acid by catalytic hydrogenation,[79] hydride reduction[81,82] of derivatives, or reduction by electrochemical methods[83] (Figure 15). Reduction of N-Cbz-methyl-L-glutamate[84] and cyclization of a γ-

chloro norvaline derivative[85] also provide routes to L-proline. A synthesis of *R* and *S* proline employing a cobalt (III) complex has also been reported.[80]

Figure 15. General approach to L-proline from L-pyroglutamic acid derivatives.

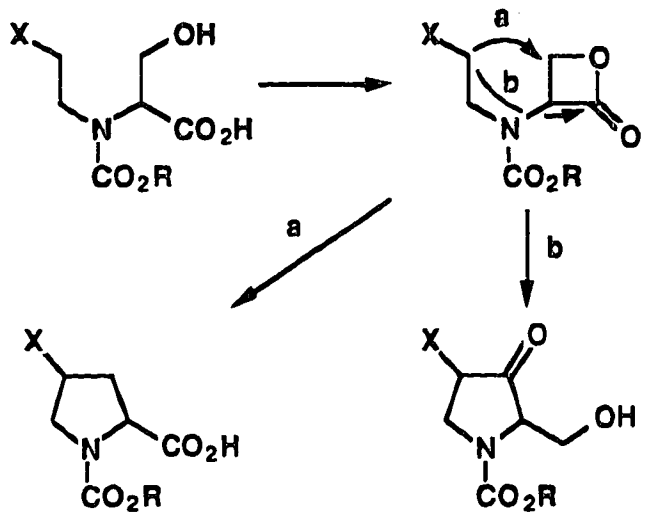


The disadvantage of the racemic syntheses is the necessity of a resolution of the racemate. The known routes to optically pure proline provide very little scope for modification and preparation of analogues that are of considerable pharmaceutical interest. For example, peptides containing bicyclic proline analogues are potent inhibitors of angiotensin converting enzyme (ACE),[177] and many related derivatives have been synthesized as intermediates for ACE inhibitors.[178] Unsaturated proline analogues are effective tools to study structure activity relationships[179] and conformational properties[180,181] of biologically important peptides of which proline is a constituent. Several other analogues of proline occur naturally.[1] Hence development of a general synthetic strategy that would lead to a functionalized proline suitable for further manipulation seems highly desirable.

Previous studies[67-69] show that β-lactones derived from L-serine are versatile intermediates in amino acid synthesis and can be regiospecifically opened at the β-carbon

by nucleophiles. An appropriately modified serine β-lactone would be a convenient precursor to proline if an intramolecular cyclization of the protecting group on the nitrogen proceeds regiospecifically at the β-carbon of the lactone (Path a, Scheme 27). Cyclization at the carbonyl (Path b, Scheme 27) would give a functionalized prolinol which may be oxidized to a proline derivative.

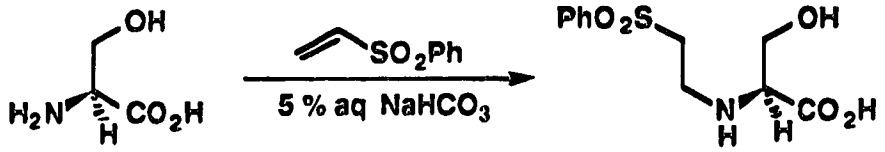
Scheme 27.



X = electron withdrawing group

Initial studies aimed towards the synthesis of a suitably N-modified serine derivative (Scheme 27) that could be used to synthesize the key intermediate lactone. Michael-type reaction of phenyl vinyl sulfone[182-186] and L-serine in basic medium by modification of the literature procedure[182] provides a protected serine **55** in 60% yield (Scheme 28).

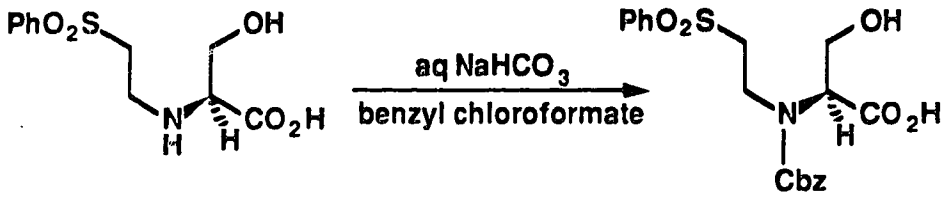
Scheme 28.



L-Serine 55

Further protection of compound **55** with benzyl chloroformate gives the fully protected serine derivative **56** (Scheme 29).

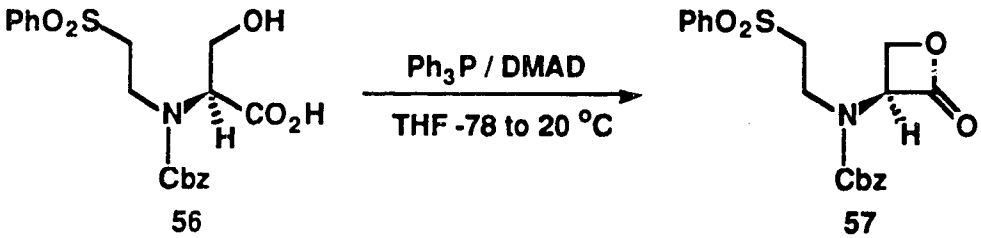
Scheme 29.



55 56

This protected serine derivative cyclizes to the target β-lactone **57** in ~50% yield (Scheme 30) using the known Mitsunobu procedure developed in our laboratories.[67]

Scheme 30.

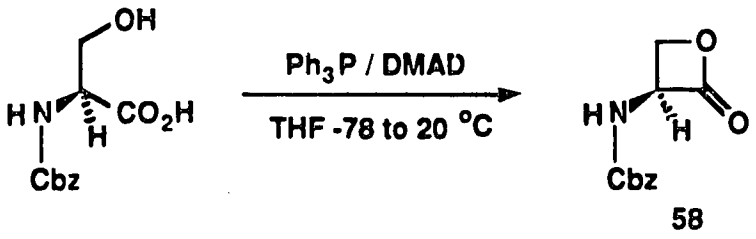


56 57

The above synthetic sequence (Schemes 28-30), although successful in producing sufficient amounts of β-lactone **57**, is cumbersome due to the low yield for conversion of **55** to **56** (Scheme 29). Reactions involving the hydroxyl group of the serine may be competing at this stage and an alternative synthesis of **57** was therefore investigated.

The most direct approach to **57** would be a reaction of the N-(benzyloxycarbonyl)-L-serine β-lactone (**58**) with phenyl vinyl sulfone. Compound **58** was prepared by the known procedure[67] from commercially available N-(benzyloxycarbonyl)-L-serine (Scheme 31).

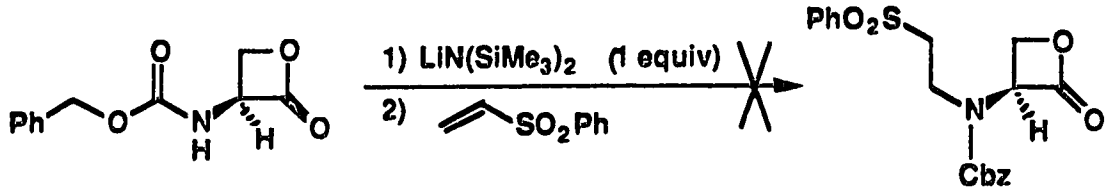
Scheme 31.



58

The reaction of **58** with phenyl vinyl sulfone in the presence of 1 equivalent of base (Scheme 32) however does not produce **57** but leads to a complex mixture of products. Possibly the basic conditions in combination with the relatively high temperatures required for N-alkylation (> -23 °C) cause intramolecular attack of the carbamate oxygen on the β-lactone.[68]

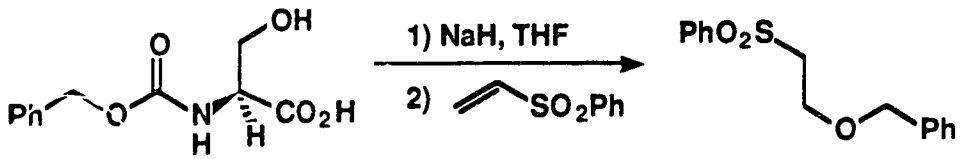
Scheme 32.



58 57

A variation involving reaction of N-(benzyloxycarbonyl)-L-serine with phenyl vinyl sulfone seemed feasible for the preparation of compound **56** since analogous N-methylation of N-(benzyloxycarbonyl) amino acids proceeds readily.[187] However, the reaction of N-(benzyloxycarbonyl)-L-serine with phenyl vinyl sulfone in the presence of sodium hydride is complex, and only the ether **59** could be isolated in 37% yield. Compound **56** was not detected (Scheme 33).

Scheme 33.

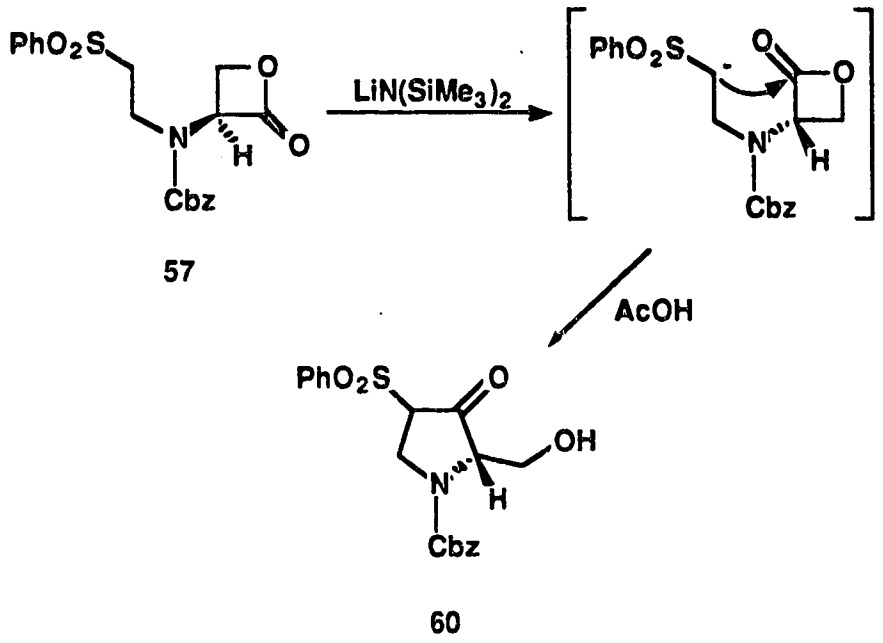


59

Compound **59** presumably arises by Michael addition of benzyl alkoxide to phenyl vinyl sulfone, indicating breakdown of the carbamate protecting group on the serine. Nevertheless, since lactone **57** is available (Scheme 30) its intramolecular cyclization was examined.

Treatment of **57** with 1 equivalent of $LiN(SiMe_3)_2$ at -78 °C for 2 h followed by a quench with acetic acid gives **60** as the major product (61%) arising from nucleophilic attack at the carbonyl carbon of the β-lactone (Scheme 34).

Scheme 34.



57

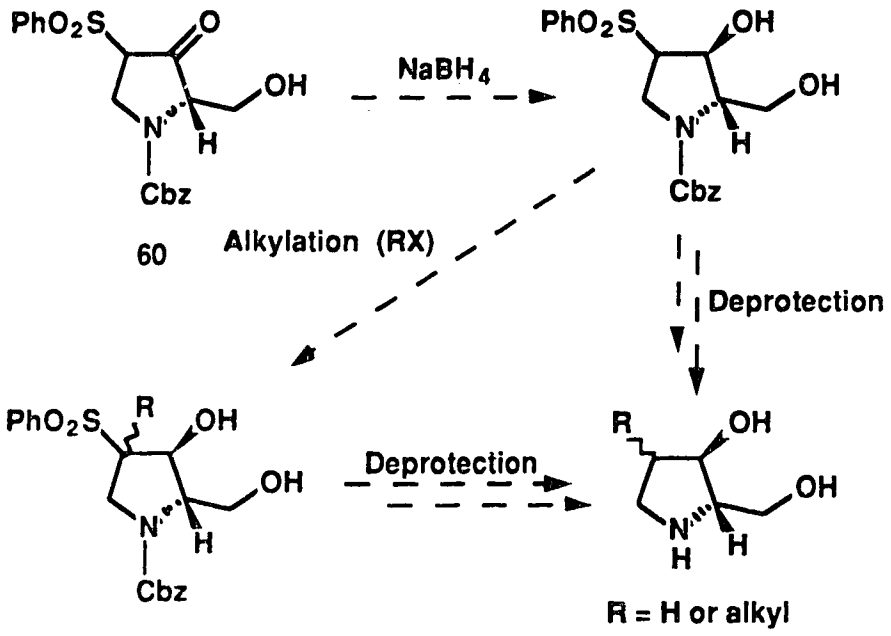
60

Earlier work on β-propiolactone indicates that carbanions (Grignard reagents, organolithium reagents) attack the carbonyl of the lactone,[188,189] unless Cu (I) salts are added, in which case ring opening occurs at the β-carbon.[68] However, CuBr· (SMe_2)[190] or CuCN[191,192] did not affect the conversion of **57** to **60** significantly and no 'proline-type' product (Scheme 27, path a) could be isolated. Apparently, in these cases intramolecular cyclization of the carbanion, once it is formed, is much faster than its conversion to the corresponding organocuprate derivative.

Unfortunately compound **60** was very unstable and attempted derivatization (e.g. formation of the *tert*-butyl dimethysilyl ether) led to decomposition. For this reason and

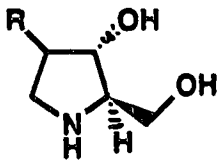
because the cyclization did not occur as anticipated, the synthesis was not examined further. However, compound **60** may still be a useful synthetic intermediate. For example reduction of the ketone with sodium borohydride to give a diol, may be stereospecific. Deprotection of the diol or further modification of the ring followed by deprotection would give substituted hydroxylated pyrrolidine derivatives (Scheme35).

Scheme 35.



The (2*R*, 3S)-2-hydroxymethyl-3-hydroxy pyrrolidine (Figure 16, R=H) is a natural product isolated[193] from seeds of the legume *Castanospermum australe* and inhibits some glucosidases.[194]

Figure 16. Naturally-occurring polyhydroxypyrrolidine derivatives



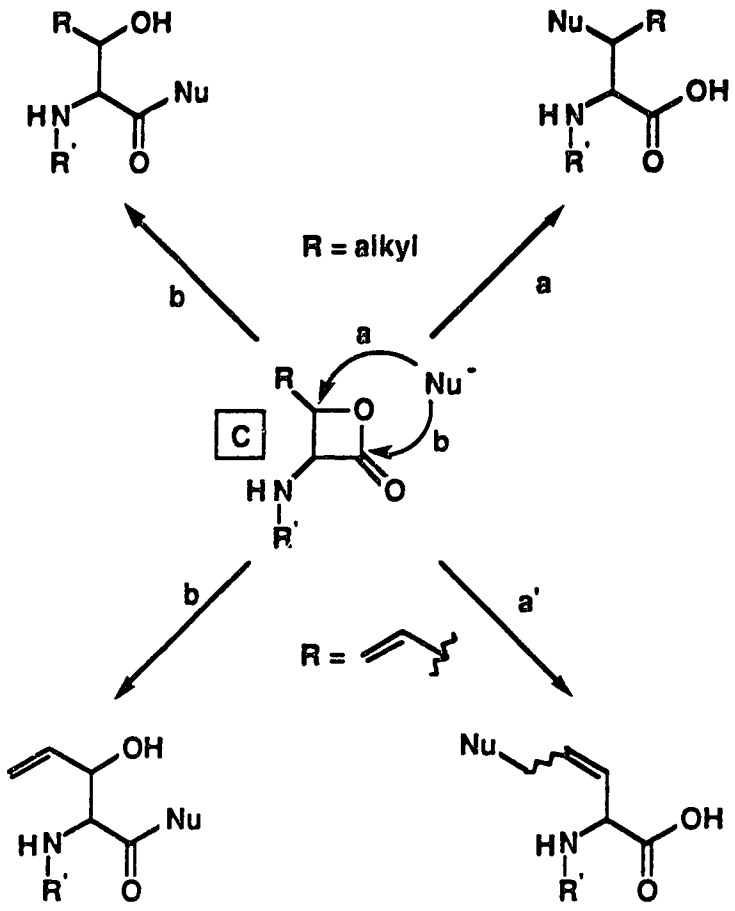
R = H, OH

Another polyhydroxypyrrolidine (Figure 16, R=OH), occurs in the fruits of *Angylocalyx boutiqueans*.[195] Compound **60** may therefore be useful for the synthesis of polyhydroxy pyrrolidines some of which occur naturally and have interesting biological properties.

Synthesis and Reactivity of β-Lactones Derived from L-Threonine and Related Amino Acids

The importance of α-amino acids has prompted the recent development of numerous methods for their stereospecific synthesis.[13-29] Of the known amino acids, β–disubstituted-α-amino acids[1-3] are unique due to the presence of two adjacent chiral centers in the molecule. In addition to β-disubstituted amino acids, β,γ-unsaturated amino acids are also an important class of compounds, some of which are natural products possessing antibiotic and enzyme inhibitory properties.[129-135] An attractive approach to the synthesis of both these types of α-amino acids is by reaction of nucleophiles at the β-carbon of β-substituted α-amino-β-lactones (Path a, Scheme 36). Attack of the nucleophile at the carbonyl of the lactone (Path b, Scheme 36) is potentially also possible, and appropriate reaction conditions would have to be developed to avoid this.

Scheme 36.

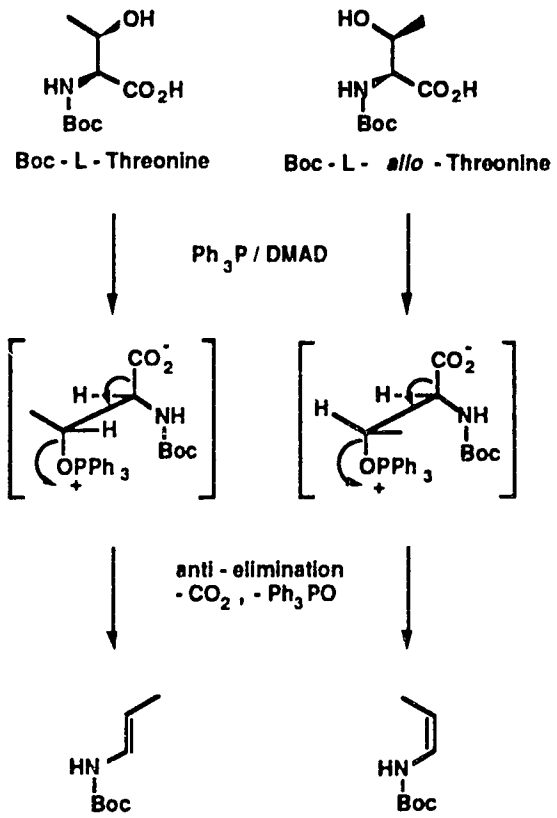


Earlier work[67-69] shows that N-protected β-lactones derived from serine (for example β-lactone **58**) afford access to stereochemically pure α-amino acids upon reaction with a variety of carbon or heteroatom nucleophiles. The proposed route (Scheme 36) should also provide β-disubstituted α-amino acids with control of chirality at both centers. This approach seems especially promising because a number of methods for production of stereochemically pure β-hydroxy amino acids have been developed.[110-124] In addition, the commercial availability of the pure L- and D- isomers of both threonine and *allo*-threonine suggests that many β-methyl amino acids that occur naturally[1] or are useful tools for biochemical studies. For example, β-halo-α-aminobutyrates[66,93-101] might be easily

obtained by this approach. The synthesis of a suitably N-protected β-lactone derived from either threonine or *allo*-threonine (Scheme 36, structure C, R = CH_3) was therefore investigated.

Previous studies[196] show that low temperature (-78 °C) Mitsunobu conditions (Ph_3P/DMAD), which are successful for cyclising N-(*tert*-butoxycarbonyl) (Boc) serine, give only stereospecific decarboxylative anti elimination when applied to Boc-L-threonine and Boc-L-*allo*-threonine, to produce the *(E)* and *(Z)* enamines respectively (Figure 17).

Figure 17. Decarboxylative dehydration of Boc-L-threonine and Boc-L-*allo*-threonine under low temperature Mitsunobu conditions.

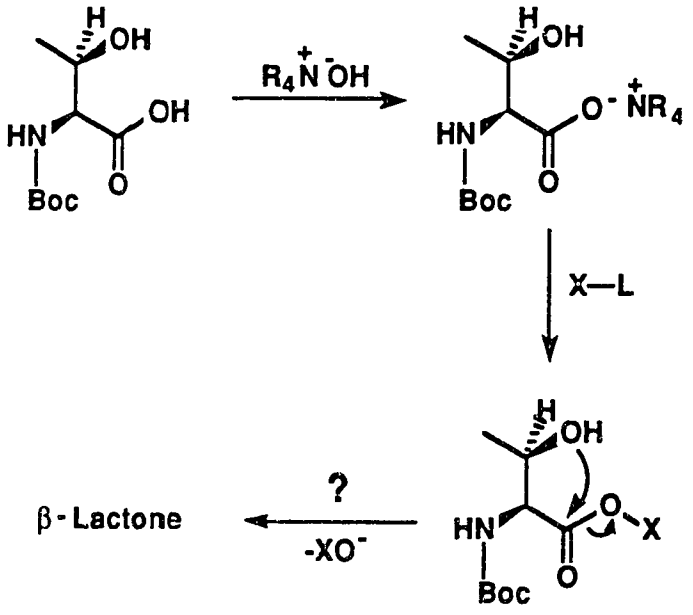


Since Mitsunobu cyclization of β-hydroxy acids bearing a protected α-amino substituent proceeds exclusively by hydroxyl group activation,[70] in contrast to certain alkyl substituted

analogues,[197] it appears that replacement of hydrogen by methyl hinders nucleophilic displacement sufficiently to completely shift partitioning of the key phosphonium intermediate toward elimination (Figure 17). Hence a reagent which gives carboxyl group activation seems advantageous. Previous syntheses[87] of N-protected threonine β-lactones which employ carboxyl group activation (DCC, DMAP) or hydroxyl group activation (from DL-O-tosyl allo-threonine, Figure 8) proceed in very low yield (0.8% and 1.6% respectively).

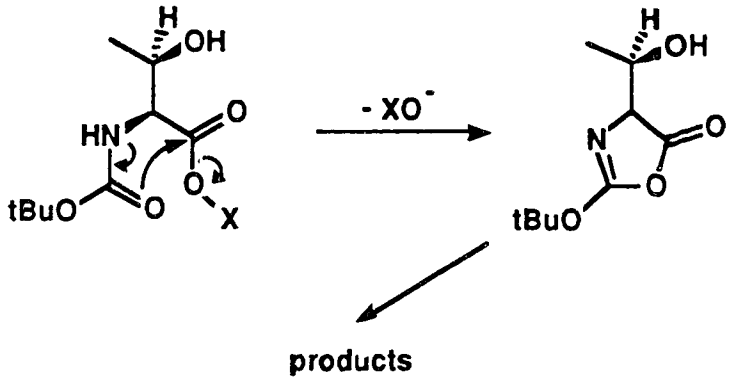
Treatment of a suitably N-protected threonine derivative with an 'activating' reagent could lead to an indiscriminate reaction with both the carboxyl and hydroxyl group. However, conversion of the carboxyl to the nucleophilic carboxylate should increase its nucleophilicity and render it more reactive than the hydroxyl.[198] Hence in initial studies, a tetraalkylammonium salt of Boc-L-threonine was chosen as the starting material (Scheme 37).

Scheme 37.



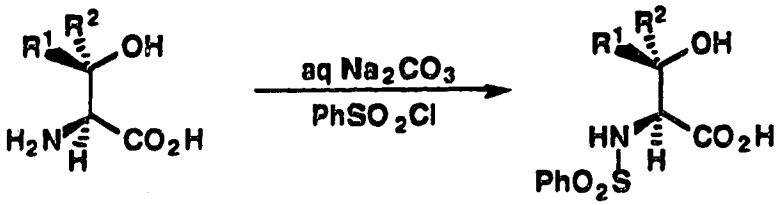
The use of a tetraalkylammonium salt seemed promising since such species had previously been converted to esters under mild conditions.[199-201] Treatment of the tetraethylammonium salt of Boc-threonine with a variety of activating reagents (e.g. tosyl chloride, triflic anhydride, trichloroethyl chloroformate,[202] followed by a base (e.g. aqueous ammonia, DBU, potassium carbonate) to promote cyclization of the mixed anhydride intermediate gives complex reactions and no β-lactone can be detected. Variation of temperature (-78 °C, 20 °C, refluxing acetone) has no useful effect on the reaction. The inability of these procedures to generate any β-lactone is presumably because of competing oxazolinone formation[203-205] (Scheme 38). This seems quite likely since in one report[206] the use of an N-(2-nitrobenzene*sulfenyl*) group and carboxyl activation afforded a threonine β-lactone derivative as an undesired side product in low yield. With other nitrogen protecting groups no β-lactone was observed.

Scheme 38.



To prevent this involvement of the protecting group in the reaction, the N-benzenesulfonyl derivatives[207] of L-threonine (**61**) and L-*allo*-threonine (**62**) were examined. These are readily available by reaction of L-threonine and **L**-*allo*-threonine with benzenesulfonyl chloride by adaptation of the literature procedure[207] (Scheme 39).

Scheme 39.

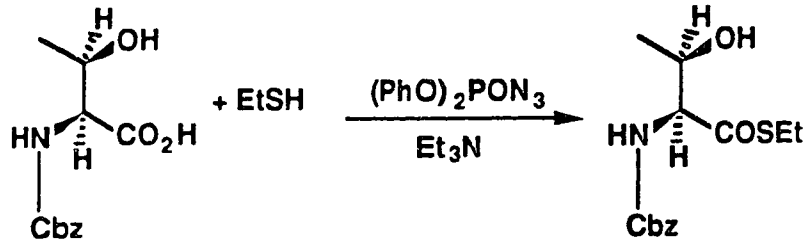


$R^1 = CH_3, R^2 = H$ (L-Threonine) 61 $R^1 = CH_3, R^2 = H$

$R^1 = H, R^2 = CH_3$ (L-*allo*-Threonine) 62 $R^1 = H, R^2 = CH_3$

Treatment of compound **61** with dicyclohexylcarbodiimide (DCC) gives a complex mixture. The use of 1-hydroxybenzotriazole has no significant influence in the above reaction. An earlier study indicates that N-(benzyloxycarbonyl)-L-threonine can be converted to its thioethyl ester in good yield[208] by use of diphenyl phosphoroazidate[209] as the coupling reagent (Scheme 40).

Scheme 40.



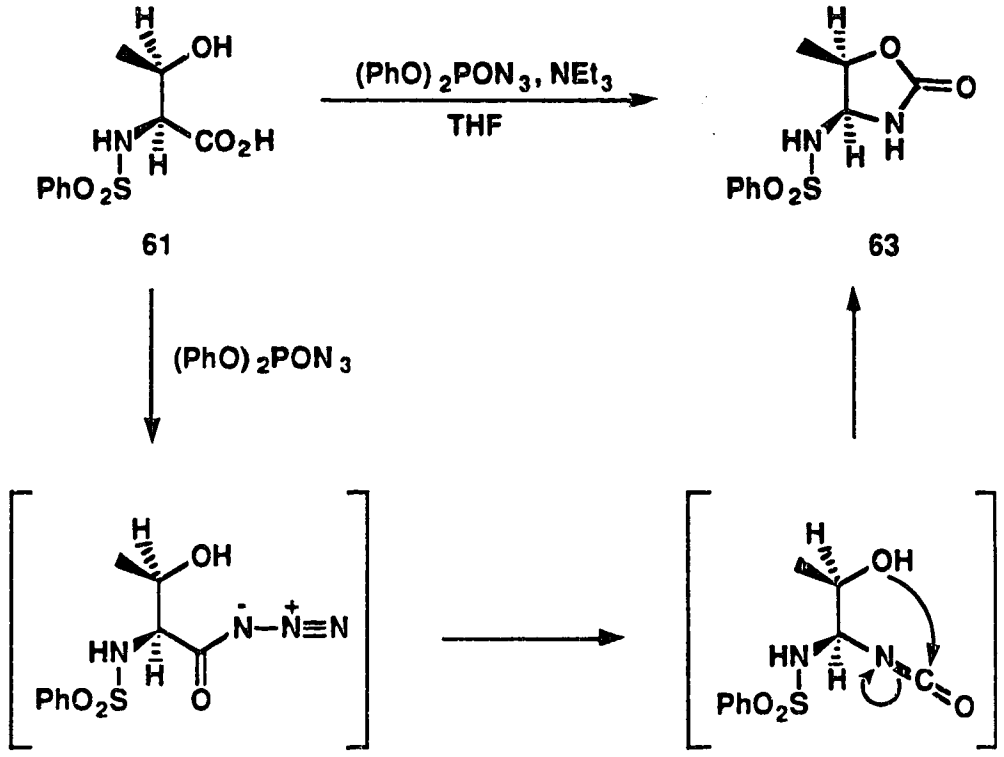
N-Cbz-L-Threonine

N-Cbz-L-Threonine thioethyl ester

It seemed quite likely that if a similar reaction were done on the threonine derivative **61** in the absence of an external nucleophile, intramolecular cyclization by the hydroxyl group would produce the requisite β-lactone. However, treatment of a THF solution of **61**

with diphenyl phophoroazidate gives exclusively the oxazolidinone **63** (42% yield, Scheme 41).

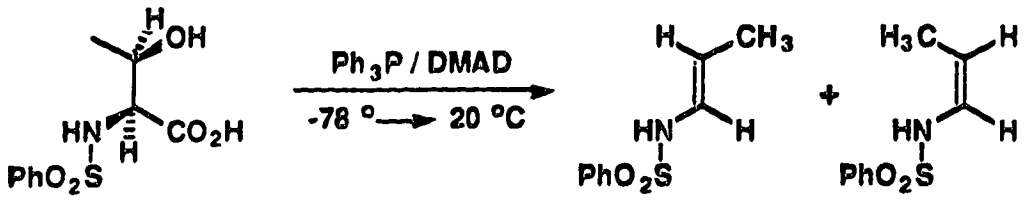
Scheme 41.



Presumably reaction of **61** with diphenylphoroazidate produces the corresponding acyl azide. This undergoes a facile Curtius rearrangement[210] to produce the isocyanate which immediately reacts intramolecularly to give oxazolidinone **63**. Similar rearrangement and cyclization of a Boc-L-serine hydroxamic acid has been observed[206] upon treatment with triphenylphosphine/diethyl azodicarboxylate.

Attempted cyclization of **61** using low temperature (-78 °C) Mitsunobu conditions leads to decarboxylative elimination, as observed for Boc-threonine[196] and produces the unstable enamines **64a** *(E)* and **64b** *(Z)* in approximately 5:1 ratio (45% yield, Scheme 42).

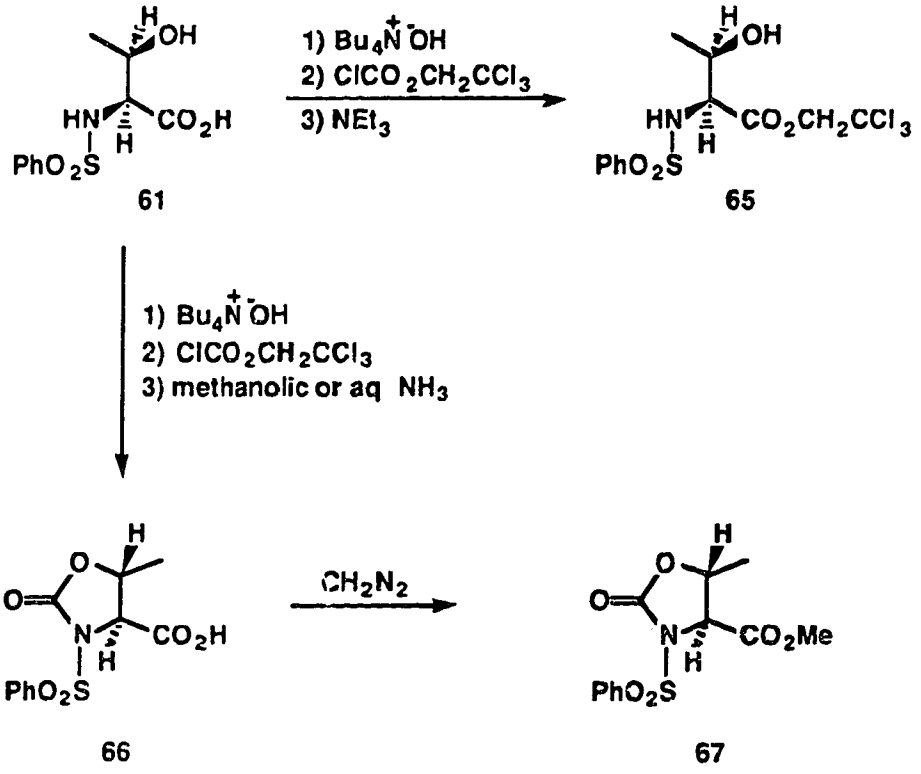
Scheme 42.



61 64a 64b

Cyclizations of the tetrabutylammonium salt of **61** were also attempted. Treatment of the salt with reagents such as triflic anhydride, mesyl chloride and trichloroacetyl chloride produced no β-lactone. Reaction of the salt with trichloroethyl chloroformate followed by addition of triethylamine gives the trichloroethyl ester **65** (19%, Scheme 43).

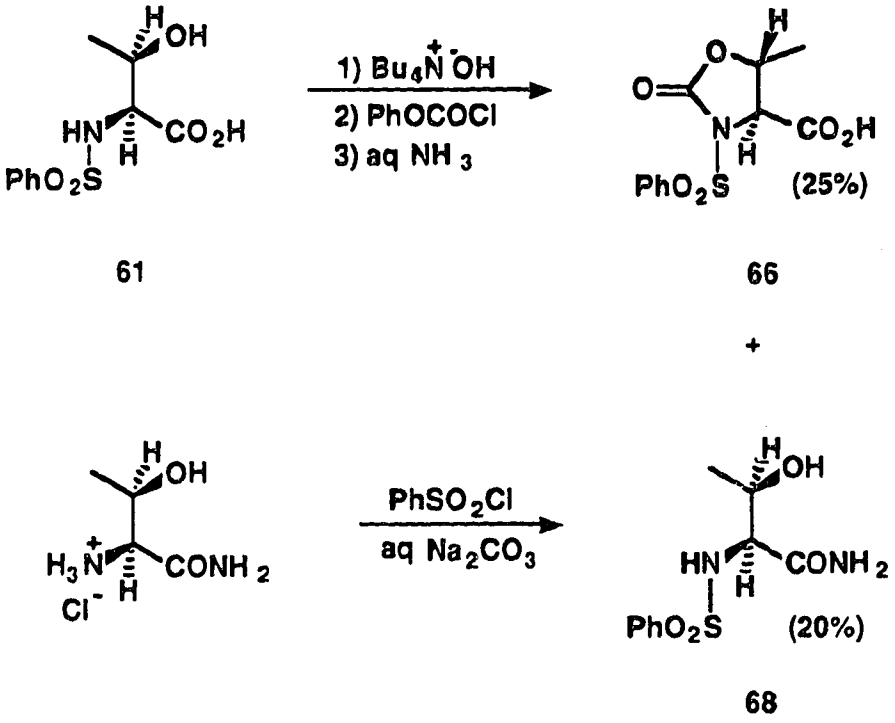
Scheme 43.



61 65 66 67

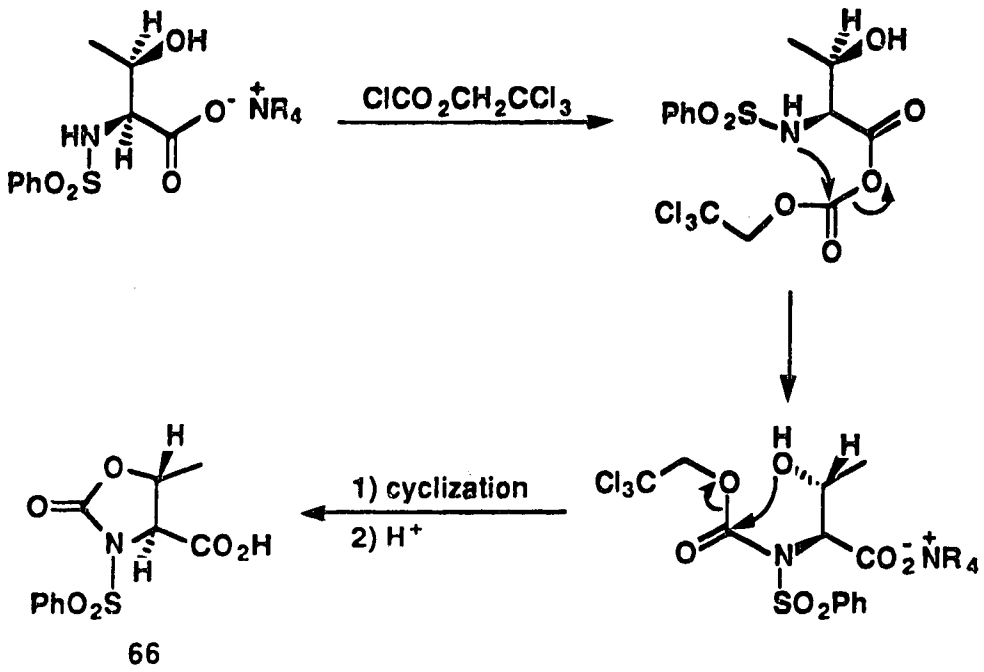
In a similar process, addition of excess aqueous or methanolic ammonia (instead of triethylamine) produces the carboxyoxazolidinone **66** in 98% yield. This was converted to its methyl ester **67** for structure confirmation (Scheme 43). Phenyl chloroformate/aqueous ammmonia in an analogous reaction produces **66** and the amide **68** in about 1:1 ratio. The structure of **68** was confirmed by synthesis from commercially available L-threoninamide hydrochloride by modification of the literature procedure[207] for protection of the amino group (Scheme 44).

Scheme 44.



The formation of the trichloroethyl ester **65** and the amide **68** is indicative of carboxyl group activation in these reactions. Formation of oxazolidinone **66** may be rationalized by an acyl transfer from the mixed anhydride, obtained from **61**, to the nitrogen followed by ring closure (Scheme 45).

Scheme 45.



An attempt to react the tetrabutylammonium salt of **61** with triphenylphosphine/dimethyl azodicarboxylate was unsuccessful, and unreacted **61** was isolated.

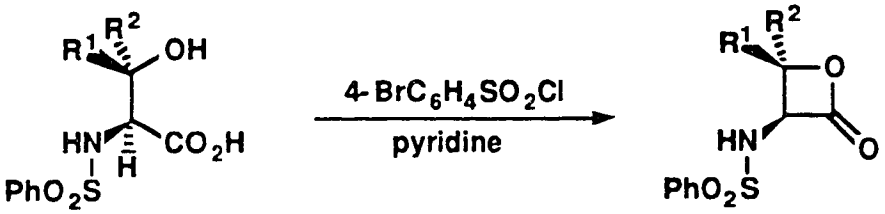
In order to achieve carboxyl group activation without derivatization, a pyridine solution of **61** was treated with benzenesulfonyl chloride. A small amount of the required β-lactone **69** is indeed formed, and can be isolated in ~20% yield, although these conditions are usually applicable only for the preparation of tri- and tetra-substituted β-lactones.[211-213] Several modifications of this procedure were attempted with different activating reagents, for example, tosyl chloride, mesyl chloride[214] and other substituted arylsulfonyl chlorides. The results are summarized in Table 5.

Table 5. Reagents for the lactonization of N-(benzenesulfonyl)-L-threonine.

Starting material	Activating reagent	Lactone yield (%)
61	$PhSO_2Cl$	20
61	CH_3SO_2Cl	18
61	$pMeOC_6H_4SO_2Cl$	—
61	$pNO_2C_6H_4SO_2Cl$	19
61	$pClC_6H_4SO_2Cl$	34
61	$pBrC_6H_4SO_2Cl$	40-55

Treatment of **61** with 4-bromobenzenesulfonyl chloride in pyridine at -40 to -15 °C gives the corresponding lactone **69** in 40 to 55% isolated yield. The reaction is also applicable to the *allo*-threonine derivative **62** to produce the lactone **70** in 55% yield (Scheme 46).

Scheme 46.



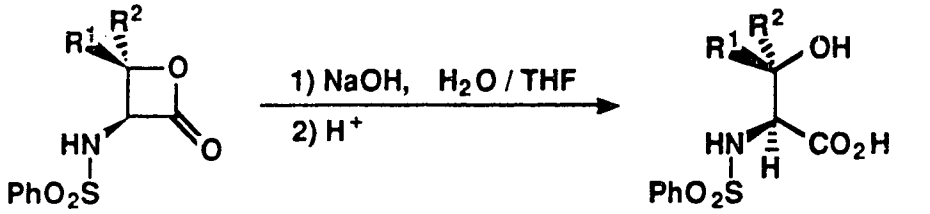
61 $R^1 = CH_3, R^2 = H$
62 $R^1 = H, R^2 = CH_3$

69 $R^1 = CH_3, R^2 = H$
70 $R^1 = H, R^2 = CH_3$

The cyclization conditions are fairly specific and variation in activating reagent (Table 5), solvent composition (e.g. THF or CH_3CN as cosolvents, use of collidine instead of pyridine), or temperature drastically lowers the yield of **69**.

The stereochemistry of lactones **69** and **70** is confirmed by their ^1H NMR spectra. The coupling constants of the α and β hydrogens are 6.0 Hz for the *cis* β-lactone **69** and 3.8 Hz for the *trans* β-lactone **70**. These values are in good agreement with reported values[89,215] for such disubstituted lactones. Hydrolysis of **69** and **70** by aqueous base gave diastereomerically pure **61** and **62** (Scheme 47). Since it is known that under these conditions ring opening occurs by attack at the carbonyl without alteration of the configuration at the β-carbon,[70,126,216-218] the transformation of **69** to **61** and **70** to **62** verifies the structural assignment.

Scheme 47.



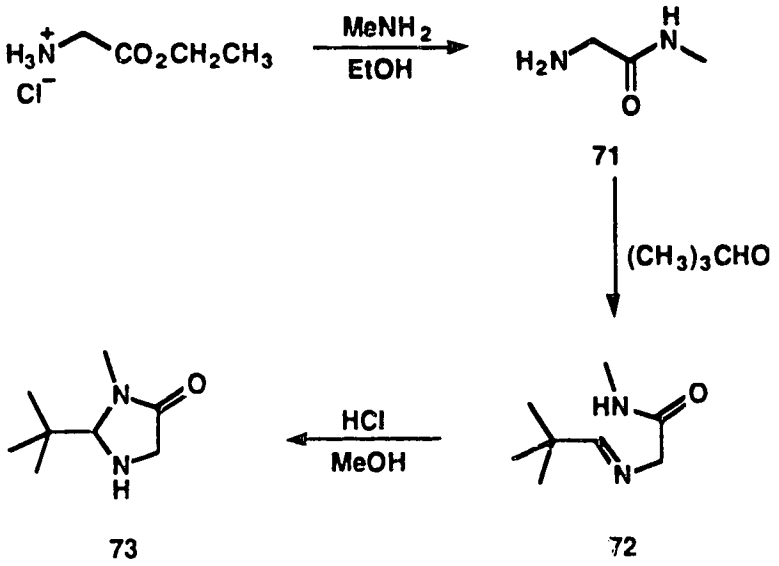
69 $R^1 = CH_3, R^2 = H$
70 $R^1 = H, R^2 = CH_3$

61 $R^1 = CH_3, R^2 = H$
62 $R^1 = H, R^2 = CH_3$

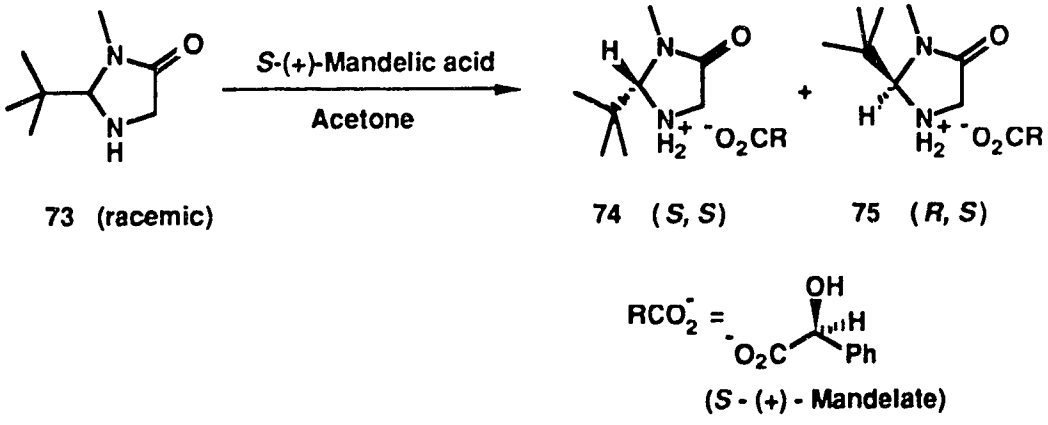
In order to test the general applicability of the lactonization procedure, cyclization of a different β-hydroxy amino acid was investigated. The requisite stereochemically pure β-hydroxy amino acid was synthesized using a chiral glycine enolate derivative of Seebach and coworkers.[114] Treatment of commercially available glycine ethyl ester hydrochloride with methylamine according to the literature procedure gives N-methyl glycinamide **71**. Reaction of the amide **71** with pivaldehyde affords the imine **72** which cyclizes upon

exposure to methanolic HCl to the racemic imidazolidinone **73** (Scheme 48).[219] The imidazolidinone **73** is then resolved by the literature procedure[220] by using *S* (+) mandelic acid. The '*S*' imidazolidinone crystallizes as the (*S*, *S*) diastereomeric salt **74** while the (*R*, *S*) diastereomeric salt **75** stays in solution (Scheme 49).

Scheme 48.

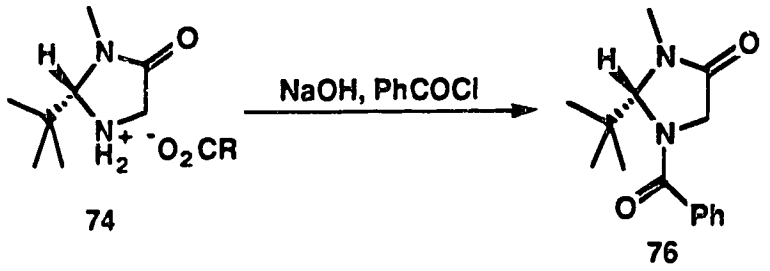


Scheme 49.



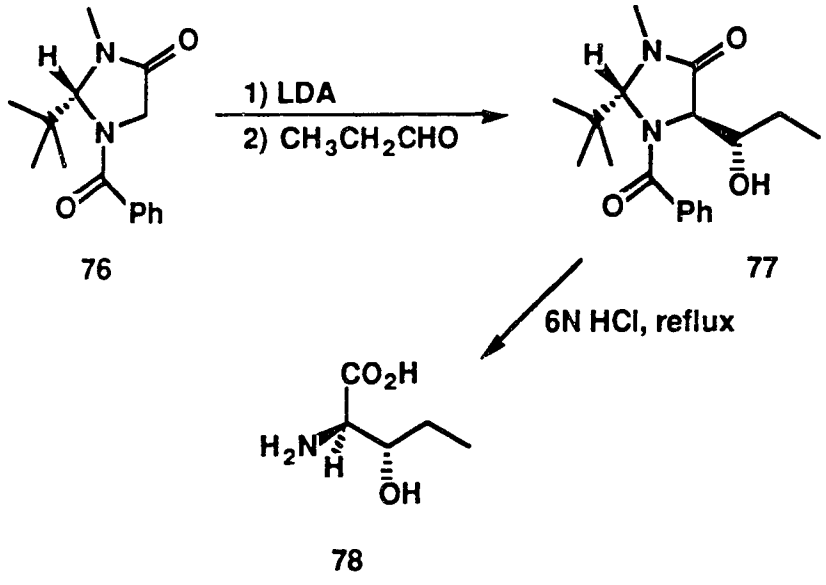
Benzoylation converts the (*S*, *S*) diastereomeric salt **74** to the requisite optically pure imidazolidinone **76** (Scheme 50).

Scheme 50.



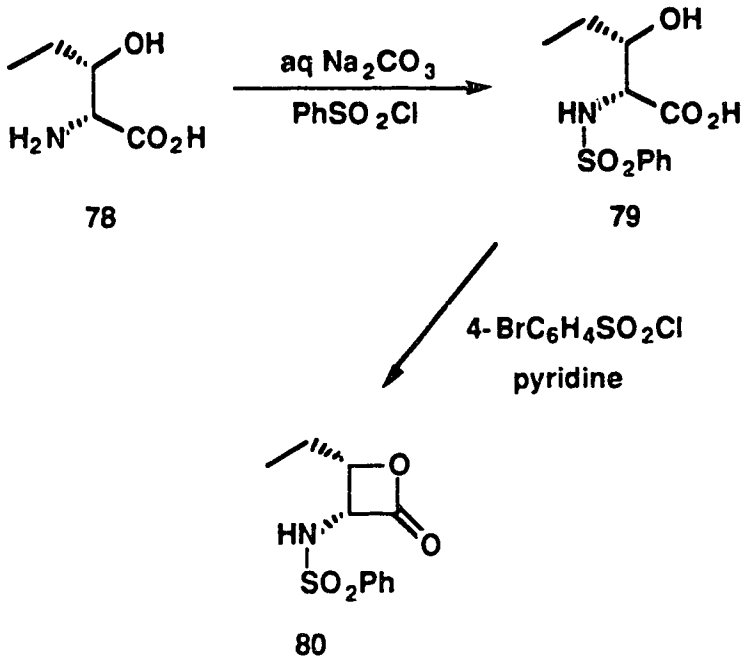
Condensation of imidazolidinone **76** with propionaldehyde by modification of the literature procedure[114] gives **77** which is readily hydrolysed to the requisite (2*R*, 3S)-2-amino-3-hydroxypentanoic acid **78** (Scheme 51). The stereochemical assignment of **78** is based on extensive precedent[114] for such aldol condensations of **76**.

Scheme 51.



Protection of **78** with benzenesulfonyl chloride[207] gives the corresponding N-benzenesulfonyl derivative **79** which cyclizes to the β-lactone **80** (39% yield) using 4-bromobenzenesulfonyl chloride in pyridine as described for **61** and **62** (Scheme 52).

Scheme 52.

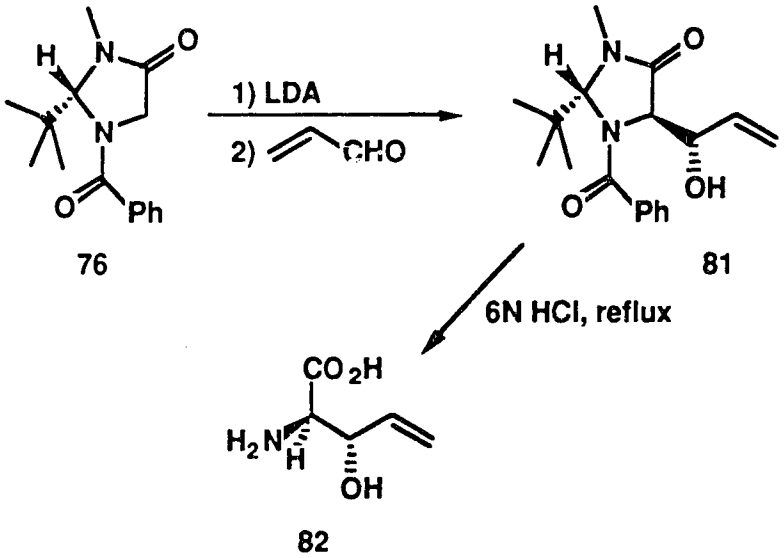


The stereochemistry of lactone **80** is confirmed by its ^{1}H NMR spectrum. The coupling constant of 6 Hz for the α and β hydrogens indicates a cis stereochemistry[215] as shown. Since the cyclization of **79** proceeds by carboxyl group activation, this also defines the relative stereochemistry of the hydroxyl and amino substituents in **78**. The synthesis of **80** demonstrates the general applicability of the lactonization procedure to β-alkyl substituted β-hydroxy amino acids.

Since β-vinyl lactones are also of interest as synthetic intermediates (see Scheme 36), the preparation of a β-hydroxy-β, γ-unsaturated amino acid was undertaken. A

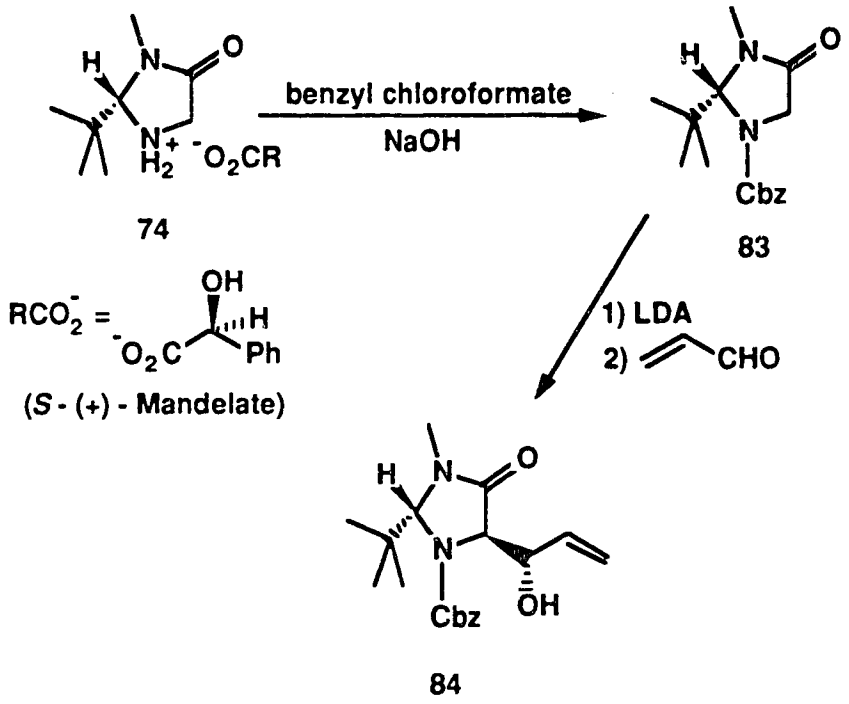
previous investigation reported an allylic oxidation of a derivative of commercially available allyl glycine to the corresponding β-hydroxy derivative.[221] However, the procedure involves extensive derivatization and tedious separation of diastereomers. In addition, enantiomerically pure allyl glycine is extremely expensive ($ 90.85/g for L-allylglycine (Sigma)). Hence diastereospecific synthesis of β-hydroxy-β, γ-unsaturated amino acid derivatives was examined using the chiral glycine enolate derivative of Seebach and coworkers. Reaction of **76** with acrolein by modification of the literature procedure[114] gives the condensation product **81** in 82% yield. Although deprotection of **81** using the general literature procedure (6 N HCl, reflux) leads to partial decomposition, the free β-hydroxy amino acid **82** could be isolated in 67% yield (Scheme 53). Unfortunately the reaction is not reproducible and the yield varies in repeated preparations. The product has to be purified several times by ion exchange chromatography to remove polymeric side products.

Scheme 53.



Presumably, intramolecular acyl transfer from nitrogen to oxygen,[114] in **81** gives an allylic benzoate which undergoes solvolysis and extensive decomposition. To prevent this the benzoyl group was replaced by a benzyloxycarbonyl group. Thus treatment of **74** according to the literature procedure[114] with benzyl chloroformate gives **83** which can be converted to **84** by reaction with acrolein (Scheme 54).

Scheme 54.

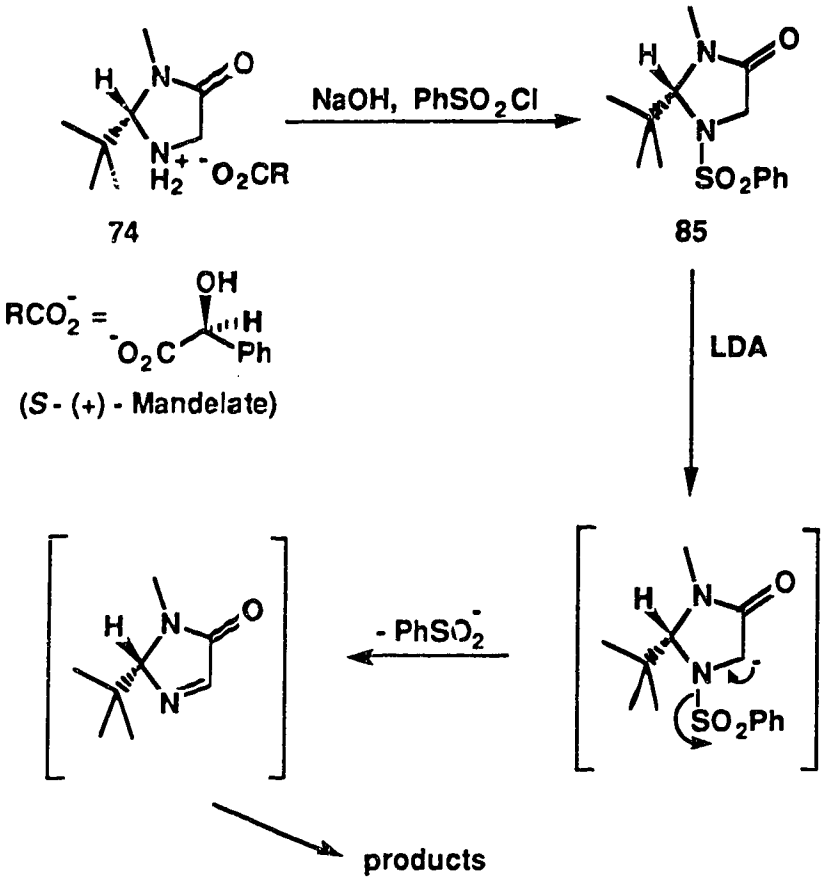


74 83 84

Acid hydrolysis of **84** affords **82** (57% yield) but decomposition products again hinder purification of **82**. Since **82** would eventually have to be protected as an N-benzenesulfonyl derivative, it seemed that introduction of this group into the chiral imidazolidinone would not only give the desired protected amino acid but would also reduce the possibility of decomposition by acyl transfer. Treatment of **74** with benzenesulfonyl chloride generates **85** in 86% yield. Unfortunately, attempted condensation of **85** with acrolein in the presence of LDA leads to decomposition. Possibly

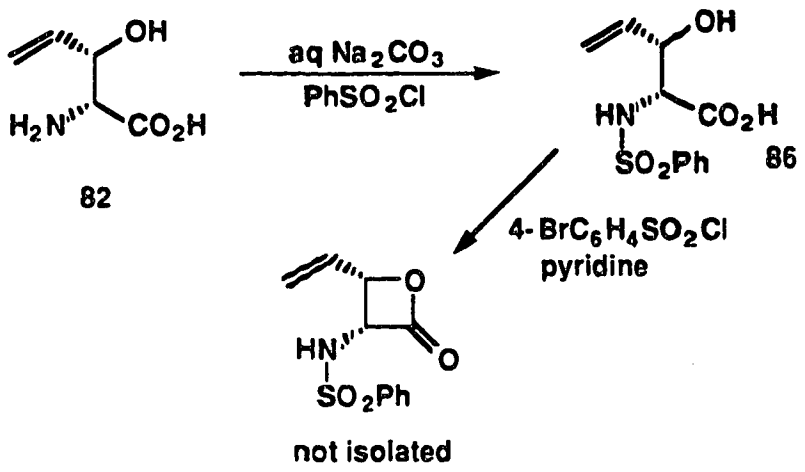
a facile elimination[222-225] of the sulfone from **85** gives an imine which then decomposes under the reaction conditions (Scheme 55).

Scheme 55.



Nevertheless, since the requisite (2*R*, 3*S*)-2-amino-3-hydroxy-4-pentenoic acid (**82**) was available from **81** and **83**, its protection and lactonization could be examined. Reaction of of **82** with benzenesulfonyl chloride by modification of the literature procedure[207] produces **86** in low yield (~15%). Treatment of **86** with 4-bromobenzenesulfonyl chloride in pyridine as described for **61**, **62**, and **79** gave several products. The required β-lactone could be detected by infrared spectroscopy ($\nu_{C=O}$ 1840 cm^{-1}) but attempted isolation led to decomposition (Scheme 56).

Scheme 56.

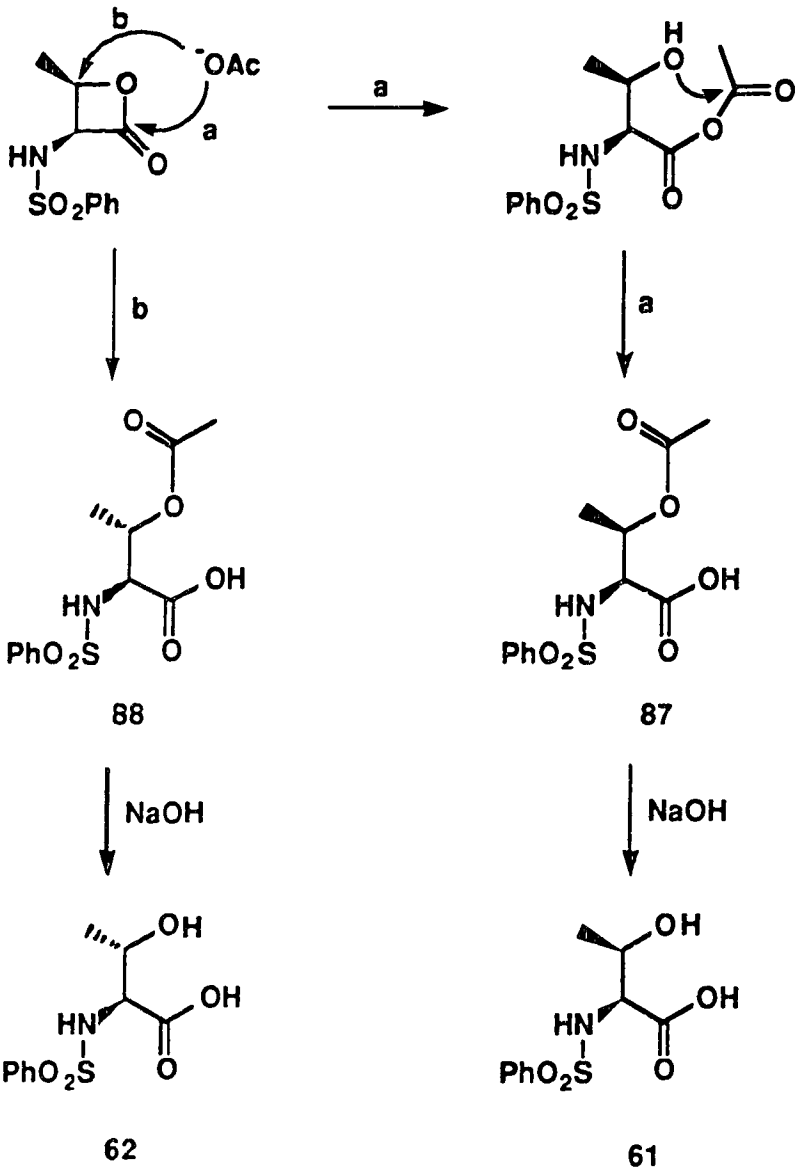


Difficulties in the preparation of the starting β-hydroxy amino acid, in its protection, and in the unstable nature of the β-vinyl lactone make this synthesis unattractive and this approach was not pursued. However, the β-alkyl-α-amino-β-lactones **69**, **70**, and **80** are readily available, and since recent investigations demonstrate that β-butyrolactones are readily attacked by a variety of nucleophiles at the β-carbon,[125,126] the reactivity of these lactones with several nucleophilic reagents was investigated.

As described earlier (Scheme 47) base (NaOH) hydrolysis of **69** and **70** produces **61** and **62**, respectively by attack of hydroxide exclusively at the carbonyl as expected. Acid hydrolysis (HCl) of **69** also affords **61**. Reaction of isomerically pure **69** with sodium acetate in acetic acid produces diastereomeric acetates **87** and **88** in a 7:1 ratio (51% yield). Hydrolysis of this mixture with aqueous base generates the N-protected threonine **61** and *allo*-threonine **62** in the same ratio. This shows that the predominant reaction of acetate is at the carbonyl carbon of the β-lactone, which is followed by ensuing acyl transfer (probably intramolecular) to the β-oxygen to give **87** (Scheme 57). The

reaction of **69** with acetate contrasts the behaviour of serine β-lactone which is attacked at the β-carbon.[70]

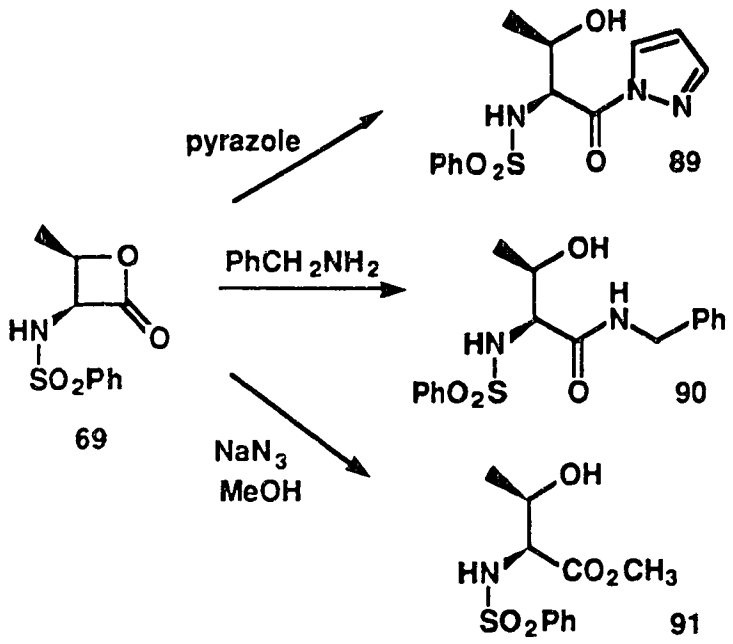
Scheme 57.



In an attempt to synthesize 2, 3-diaminobutanoic acids, some of which (the D-erythro- and L-threo- isomers) are constituents of antibiotics,[1] the reaction of **69** with

nitrogen nucleophiles was examined. Unfortunately, reaction of **69** with pyrazole and benzylamine also occurs primarily (if not exclusively) at the carbonyl to form amides **89** and **90** in 75% and 72% yield respectively. Reaction of **69** with sodium azide in methanol produced the methyl ester **91**, presumably by attack of azide at the carbonyl followed by rapid methanolysis of the acyl azide (Scheme 58). The structure of **90** was confirmed by conversion to N-(benzenesulfonyl)-L-threonine (**61**) by acid hydrolysis. These transformations of β-lactone **69** are in contrast to reactions of serine β-lactone[67] and β-butyrolactone[126] with nitrogen nucleophiles.

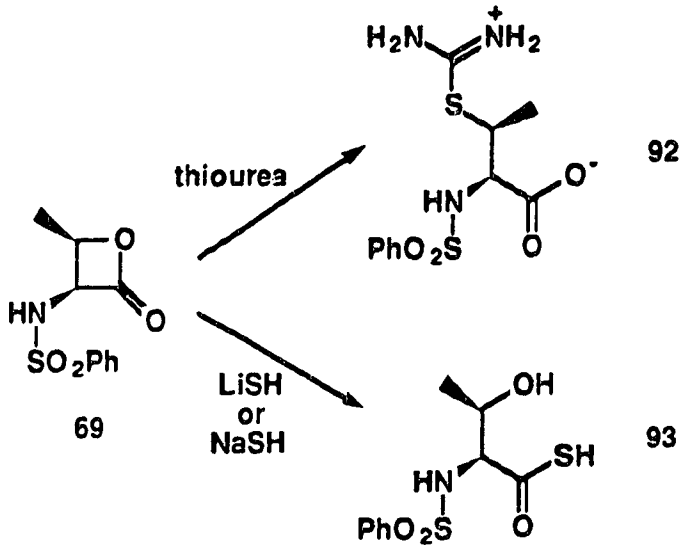
Scheme 58.



Since β-methyl cysteine[90-92] is an attractive synthetic target, reaction of **69** with sulfur nucleophiles was examined. Condensation of **69** with thiourea generates a single diastereomer of the expected isothiouronium salt **92**, a precursor of β-methyl cysteine.[226] However, LiSH or NaSH attack at the carbonyl to produce thioacid **93** (Scheme 59). The

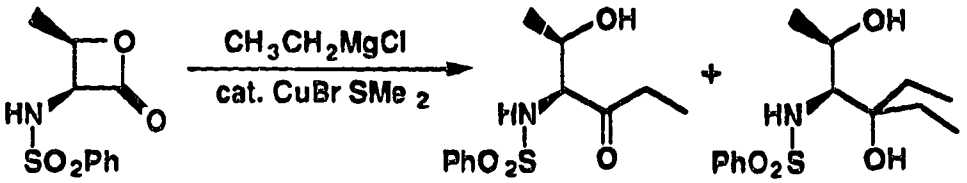
reactions of **69** with hydrosulfide anion differ from the reactions of β-butyrolactone[126] with NaSH and with thiophenol in basic medium.

Scheme 59.



Since the synthesis of β-dialkyl amino acids was of interest, reactions of **69** with carbon nucleophiles were examined next. However, copper containing organolithium reagents and organomagnesium reagents fail to give any trace of ring cleavage at the β-carbon, in contrast to the behaviour of the serine β-lactone **58**.[68] Instead treatment of **69** with ethylmagnesium chloride in the presence of catalytic CuBr·SMe_2[190] affords the ketone **94** and alcohol **95** (Scheme 60). Use of a full equivalent of CuBr·SMe_2 at -23 °C gave no reaction after several hours.

Scheme 60.



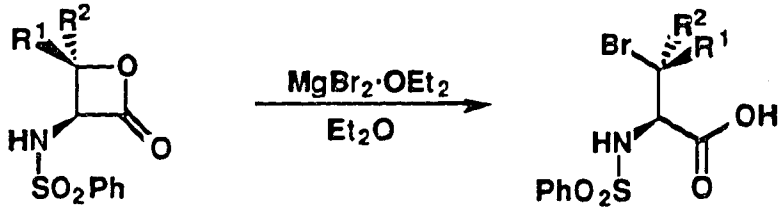
69 94 95

Similar reactions were observed with butyllithium in the presence of copper cyanide.

These transformations are in contrast to reactions of β-butyrolactone with carbon nucleophiles.[125] Apparently the additional steric and/or electron withdrawing effect of the α-nitrogen substituent on the β-lactone ring suffices to alter the course of reaction from that observed with the less substituted β-butyrolactone and serine β lactones.

However, reactions of **69**, **70**, and **80** with anhydrous magnesium halides (chloride, bromide, iodide) proceed at the β-carbon to give the corresponding β-halo amino acid derivatives in good yield. Thus treatment of **69** with $MgBr_2 \cdot OEt_2$ cleanly furnishes **96** in quantitative yield. A similar reaction of **70** produces **97**, which is diastereomeric with respect to **96** (Scheme 61).

Scheme 61.

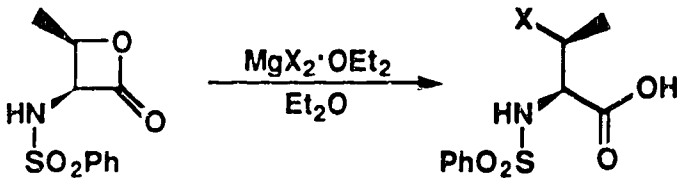


69 $R^1 = CH_3, R^2 = H$
70 $R^1 = H, R^2 = CH_3$

96 $R^1 = CH_3, R^2 = H$
97 $R^1 = H, R^2 = CH_3$

The bromo derivatives **96** and **97** are easily seen to be single diastereomers (>98%) by ^1H NMR. The stereochemistry of these products follows from comparison of relative proton chemical shifts of diastereomers **97** and **96** with **61** and **62**. It was seen that the chemical shift (δ) for the C-3 hydrogen in the *threo* series was higher than that for the corresponding hydrogen in the *allo* series (δ C-3 H is 4.5-4.6 in **97** and 4.25-4.35 in **96**). The results indicate clean inversion of configuration at the β carbon. This is also seen in the reaction of **69** with magnesium chloride and magnesium iodide which affords the products **98** and **99**, respectively, each isolated as a single diastereomer (Scheme 62).

Scheme 62.

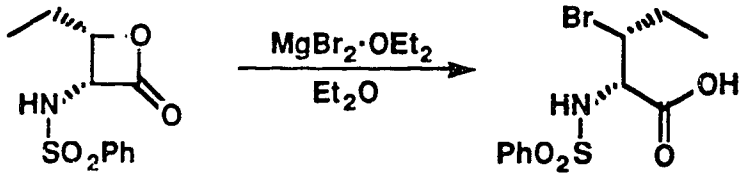


69

	X
98	Cl
99	I

Lactone **80** also reacts analogously with $MgBr_2 \cdot OEt_2$ to give the β-bromo derivative **100** in 80% yield (Scheme 63).

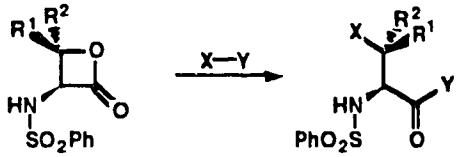
Scheme 63.



80 **100**

This reaction of the β-lactones with magnesium halides is quite rapid except with magnesium chloride, in which case added chloride ($Bu_4N^+Cl^-$) is necessary to achieve conversion at a reasonable rate. The results of reactions of **69**, **70** and **80** with nucleophiles have been summarized in Table 6.

Table 6. Nucleophilic ring opening of β-substituted β-lactones



69 $R^1 = CH_3$, $R^2 = H$
70 $R^1 = H$, $R^2 = CH_3$
80 $R^1 = CH_2CH_3$, $R^2 = H$
(enantiomer)

87 - 100

Reactants	Product[a,b] No.	R^1	R^2	X	Y	Yield[c], %
69, NaOAc	**87**	H	Me	AcO	OH	
	88	Me	H	AcO	OH	51[d]
69, pyrazole	**89**	H	Me	OH	pyrazolyl	75
69, $PhCH_2NH_2$	**90**	H	Me	OH	$NHCH_2Ph$	72
69, NaN_3, MeOH	**91**	H	Me	OH	OMe	88
69, thiourea	**92**	Me	H	$H_2\overset{+}{N}=C(NH_2)S$	O^-	70
69, LiSH	**93**	H	Me	OH	SH	84
69, NaSH	**93**	H	Me	OH	SH	86
69, EtMgCl,	**94**	H	Me	OH	Et	30
$CuBr{\cdot}SMe_2$	**95**					38

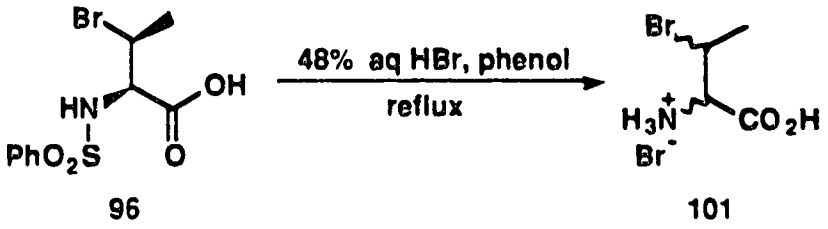
Table 6 continued

Reactants	Product[a,b]					Yield[c], %
	No.	R^3	R^4	X	Y	
69, $MgBr_2 \cdot OEt_2$	**96**	Me	H	Br	OH	99
70, $MgBr_2 \cdot OEt_2$	**97**	H	Me	Br	OH	77
69, $MgCl_2 \cdot OEt_2$ $Bu_4N^+Cl^-$	**98**	Me	H	Cl	OH	78
69, $MgI_2 \cdot OEt_2$	**99**	Me	H	I	OH	83
80, $MgBr_2 \cdot OEt_2$	**100**[c]	Et	H	Br	OH	80

[a]For structures see Scheme above Table. [b]All compounds were isolated as single pure isomers except **87** and **88**. [c]Isolated yield. [d]A 7:1 mixture of **87** and **88** was isolated. [e]Compound **80** has (2*R*, 3*S*) configuration; **100** has (2*R*, 3*R*) configuration.

Attempted deprotection of **96** by adaptation of the literature procedure[227] for such transformations (refluxing 48% aq HBr, phenol) does remove the benzenesulfonyl protecting group, but the product **101** is obtained as a 1:1 mixture of diastereomers due to nucleophilic displacement of the bromine in **96** by bromide from HBr and/or epimerisation of the α center (Scheme 64).

Scheme 64.

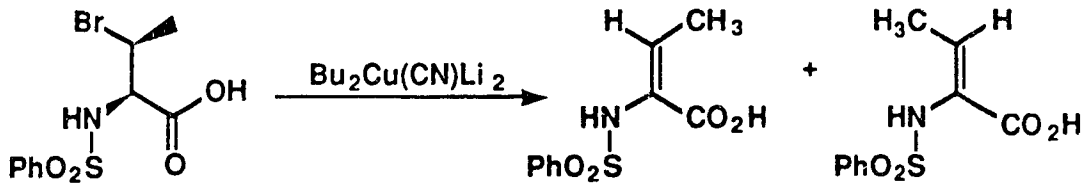


96 101

However, recent studies[228] indicate that a number of N-arylsulfonyl groups can be removed under milder conditions (HBr/AcOH at room temperature or electrolysis). The above method should therefore provide useful access to stereochemically pure β-halo amino acids for biological studies.[93-101]

A potential alternative approach to the synthesis of β-dialkyl α-amino acids involves reaction of organocuprate reagents with β-halo threonine derivatives. However, treatment of **96** with $Bu_2Cu(CN)Li_2$ at 0 °C for 3 h followed by warming to 20 °C overnight gives only elimination products. The isolated yield of the (*E*)-isomer **102** is 44% and that of the (Z)-isomer **103** is 8% (Scheme 65).

Scheme 65.



96 102 103

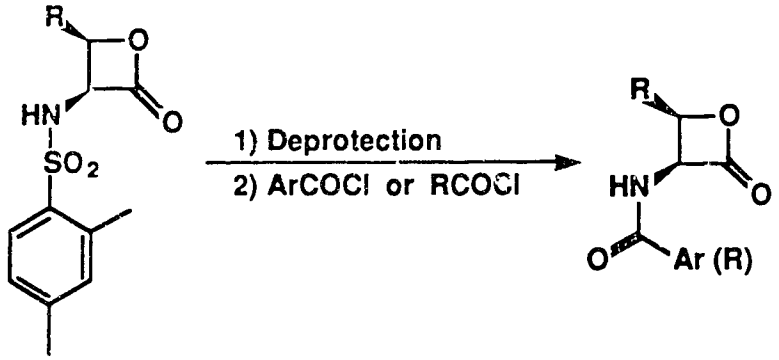
A similar reaction at -21 °C overnight gives almost exclusively **102** in 51% isolated yield (<1% (Z)-isomer) and unreacted **96** (40%). The (*E*)-isomer is the product of *anti* elimination of the elements of HBr from **96**. The increase in the amount of the (Z)-isomer

obtained at room temperature suggests that loss of stereospecifity in the elimination reaction may be due to elevated temperature. The failure of **96** to couple with organocuprate reagents contrasts behaviour of other types of secondary bromides.[192]

In summary, a synthesis of enantiomerically pure β lactones derived from threonine and related amino acids has been developed. This work demonstrates that cyclizations of β-substituted β-hydroxy α-amino acids are best accomplished by carboxyl group activation of derivatives that do not have a carbonyl group directly attached to nitrogen. Although these lactones show an unexpected tendency to undergo carbonyl attack by nucleophiles which limits their utility for synthesis of new amino acids, they do provide useful access to stereochemically pure protected α-amino acids bearing a sulfur or halogen at the β position.

Recent development[228] of more easily removable arylsulfonyl (e.g. 2, 4-dimethylbenzenesulfonyl) protecting groups may allow exchange of the substituent on nitrogen in β-substituted α-amino-β-lactones so as to generate naturally-occurring β-lactone antibiotics. The approach seems viable since the stable tosylate salt of α-amino-β-propiolactone is readily prepared from Boc-L-serine β-lactone.[69] The possibility of deprotecting the threonine β-lactone remains to be investigated (Scheme 66).

Scheme 66.

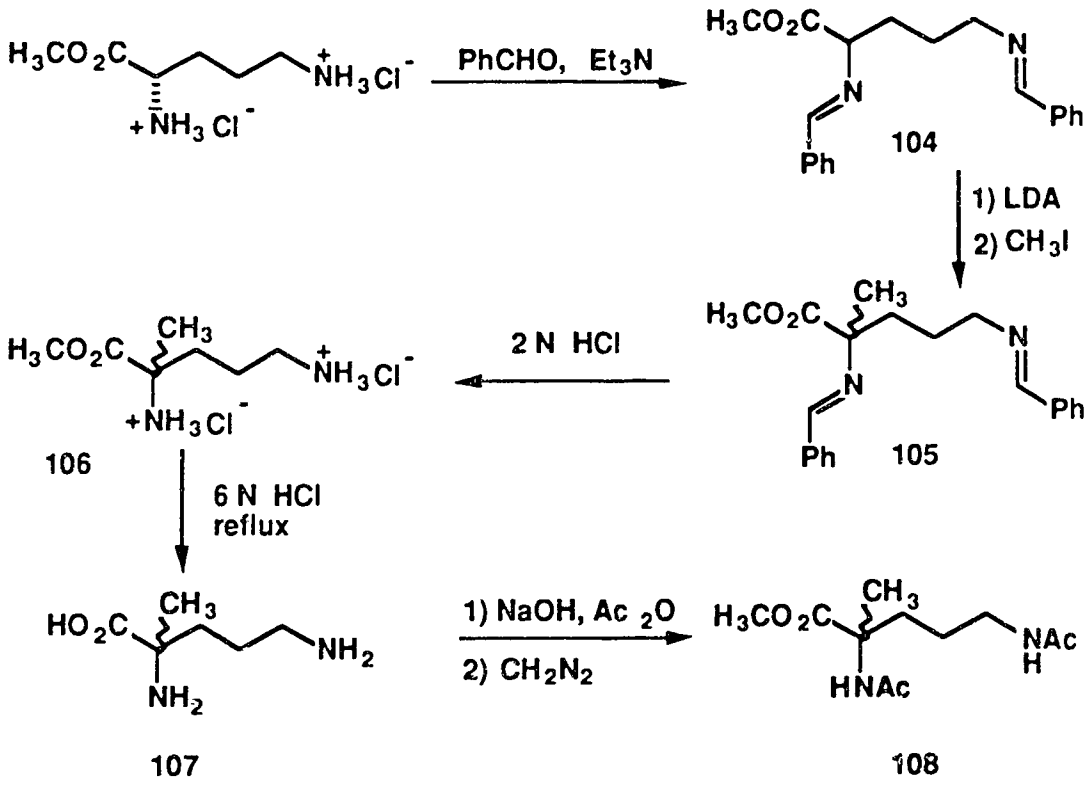


Synthesis of α-Methyl Ornithine

Methylated analogues have been shown[229] to inhibit the active transport of amino acids. Such analogues may be useful when administered with a compound that inhibits the biosynthesis of a critical amino acid, for example lysine in microbes, by interfering with uptake of the requisite amino acid from the exogenous pool. During the course of a study[230] on the inhibition of L-lysine uptake by α-methyl lysine in bacteria, it seemed helpful to determine the effect of the α-methyl analogue of a structurally related amino acid, L-ornithine.

The synthesis of the α-methyl analogue of ornithine was accomplished by adaptation of the literature procedure [231] (Scheme 67).

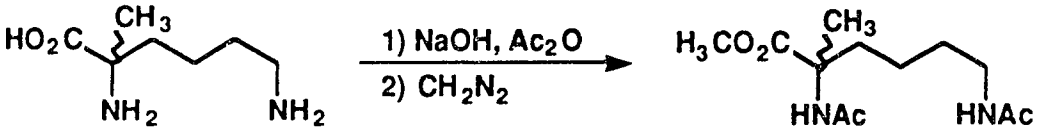
Scheme 67.



Reaction of L-ornithine methyl ester hydrochloride[232] with benzaldehyde affords the diimine **104**. Treatment of **104** with LDA followed by alkylation with methyl iodide gives **105**, which hydrolyses to α-methyl ornithine methyl ester hydrochloride **106** and subsequently to α-methyl ornithine **107**[231] upon treatment with 6 N HCl at reflux (Scheme 67).

For proper interpretation of the results of the biological studies, it is necessary to determine the amount of the parent amino acid (if any) in the α-methylated analogues. The α-methyl amino acids and the parent (α-H) compounds were therefore derivatized to form volatile compounds for gas chromatographic analysis. Acylation of the free amino acid with acetic anhydride by modification of a literature procedure[233] and esterification with diazomethane gives **108**. Derivatization of α-methyl lysine[234,235] (prepared by Dr. J. G. Kelland) as described for **107** gives the N, N'-diacetyl lysine methyl ester **109** (Scheme 68).

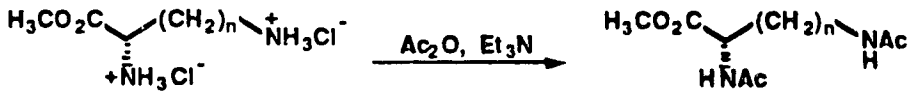
Scheme 68.



α–Methyl lysine **109**

Methyl N, N'-diacetyl ornithinate[236] **110** (prepared by Dr. J. G. Kelland) and methyl N, N'-diacetyl lysinate[237] **111** are readily prepared from the corresponding methyl ester hydrochloride salts by modification of the literature[236] procedure (Scheme 69).

Scheme 69.



n = 3, 4

110 n = 3

111 n = 4

The gas chromatographic analyses of compounds **108**, **109**, **110** and **111**, and results of the biological studies are presented in the appendix.

Conclusions.

The mild fluorinating agent (diethylamino)sulfur trifluoride (DAST) can be used to fluorinate β-hydroxy α-amino acid derivatives. The choice of a proper protecting group for the nitrogen of the amino acid is critical for successful fluorination. Carbamate protecting groups tend to undergo intramolecular cyclization reactions and are unsuitable. Benzyl esters of β-hydroxy α-amino acid derivatives in which the nitrogen is protected as a 4,5-diphenyl-4-oxazolin-2-one moiety are most suitable for successful fluorination. However the presence of a functionalized chain seems to favour dehydration of these derivatives. The fluorinated amino acid derivatives can be readily deprotected by hydrogenolysis to the corresponding free β-fluoro α-amino acids without loss of fluorine.

A modified serine β-lactone, N-(2-(benzenesulfonyl)ethyl)-N-(benzyloxycarbonyl)-L-serine β-lactone, is readily synthesized from the corresponding serine derivative. Its intramolecular cyclization involving a carbanion on the nitrogen protecting group, proceeds by attack at the carbonyl carbon of the lactone to afford a 2-hydroxymethyl-3-oxopyrrolidine derivative. Attack at the β-carbon is not observed. The presence of Cu (I) salts, known to favour attack at the β-carbon, does not affect this conversion. This

suggests that reaction of the carbanion, once it is formed, is much faster than its conversion to the corresponding organocuprate derivative.

Certain β-substituted α-amino acid derivatives (β-mercapto- and β-halo-) can be conveniently synthesized from *N*-protected α-amino β-alkyl β-lactones. These β-lactones are readily synthesized from the *N*-(benzenesulfonyl) derivaties of the parent β-hydroxy α-amino acids using carboxyl group activation by 4-bromobenzenesulfonyl chloride in pyridine. Although nitrogen, oxygen and carbon nucleophiles prefer to attack at the carbonyl carbon, sulfur (thiourea) and halogen (magnesium halides) nucleophiles react at the β-carbon with inversion of configuration to provide *N*-protected optically pure β-substituted amino acids in good yield. The synthesis of α-amino β-alkyl β-lactones may also be useful in the preparation of known and novel β-lactone antibiotics of this type.

Experimental

General

All reactions requiring anhydrous conditions were performed under a positive pressure of dry Ar using oven-dried glassware (>12 h, 120 °C) which was cooled under Ar. All organic layers obtained from extractions were dried over Na_2SO_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 solid products were dried *in vacuo* over P_2O_5 or anhydrous $CaSO_4$. Solvents for anhydrous reactions were dried according to Perrin *et al.*[238] Specifically, benzene, tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone. Acetonitrile, triethylamine and pyridine were distilled from CaH_2. Anhydrous ethyl alcohol and methyl alcohol were prepared by distilling from Mg with catalytic iodine. Solvents used for chromatography were distilled. Water used was Milli-Q (Millipore) quality, which when necessary was degassed by heating *in vacuo* and cooling under Ar. Aqueous HCl was prepared free of metal ions from Milli-Q quality water and glass distilled as constant boiling (~110 °C) 5.7 N HCl. Aqueous HBr was glass distilled before use.

All reagents employed were ACS grade or finer. Air sensitive reagents were handled under an atmosphere of dry Ar. Commercial (diethylamino)sulfur trifluoride (Aldrich) was distilled at reduced pressure (safety shield) before use (43-44 °C/8 mm). Diisopropylamine and hexamethydisilazane were distilled from CaH_2. Dimethyl azodicarboxylate was distilled at reduced pressure (safety shield) before use (71-72 °C/2 mm) and stored at 4 °C. Cuprous cyanide was obtained from Fisher Chemicals and dried *in vacuo* in an Abderhalden pistol at 64 °C over $CaSO_4$. Copper (I) bromide· dimethyl sulfide complex was prepared according to the literature procedure[190] and was recrystallized and stored in a desiccator in darkness. All commercial organometallic reagents were obtained from Aldrich Chemical Co. Organometallic solutions were periodically titrated against

menthol/phenanthroline.[239] Amino acids and amino acid derivatives used as starting materials were obtained from Sigma Chemical Co.

When possible the progress of reactions was monitored by thin-layer chromatography (TLC) using one or more of the following for visualization: UV absorption by fluorescence quenching; I_2-staining; bromocresol green spray for acids; ninhydrin spray for amino acids. All spray reagents were prepared and used as described by Krebs *et al.*[240] For TLC of amino acids on ion exchange resin sodium citrate buffers (pH 3.3 or 5.1) were used as solvents. For monitoring reactions in DMF the solvent was removed from the plate *in vacuo* before developing.

Reactions involving N-protected threonine-β-lactone and other β-lactones were monitored by TLC using bromocresol green spray (0.04% in EtOH, made blue by NaOH)[240] followed by heating of the plate for detection of the β-lactone as a yellow spot on a blue background.

Commercial thin layer and preparative layer chromatography plates were silica, Merck 60 F-254; reverse-phase, Merck RP-8F_{254} S and Macherey-Nagel and Co. ion exchange resin, Polygram^R Ionex-25 SA-Na. Silica gel for column chromatography was Merck type 60, 70-230 mesh or its equivalent from General Intermediates of Canada. Flash chromatography was performed according to Still *et al.*[241] using Merck type 60, 230-420 mesh silica gel. Normal phase medium pressure liquid chromatography (MPLC) employed a column of Merck Kieselgel 60 H (~ 60 g, 2.5 x 30 cm). Reverse phase MPLC was performed on two Merck Lobar Lichroprep RP-8 columns (size A and B) in series. All solvent mixtures are listed as volume ratios, and all medium pressure liquid chromatography was performed using solvents which were previously degassed *in vacuo*. The cation exchange resin used was BioRad AG 50 x 8 (H^+ form, 50-100 mesh).

Gas chromatography was performed on a Hewlett Packard 5890 A gas chromatograph fitted with an Alltech 10 m x 0.53 mm bonded FSOT RSL-300

polyphenylmethylsiloxane column. Compounds were detected using a flame ionization detector.

All literature compounds had IR, ^1H NMR, and mass spectra consistent with the assigned structures. Melting points are uncorrected and were determined on a Thomas Hoover or Buchi oil immersion apparatus using open capillary tubes. Optical rotations were measured on a Perkin Elmer 241 polarimeter with a microcell (10.00 cm, 0.9 mL) at ambient temperature. All specific rotations reported were measured at the sodium D line. Infrared spectra (IR) were recorded on a Nicolet 7199 FT-IR spectrometer. Mass spectra (MS) were recorded on a Kratos AEI MS-50 (high resolution, electron impact ionization), MS-12 (chemical (NH_3) ionization, CI MS), and MS-9 (fast atom bombardment with argon, POSFAB). The term 'Cleland's reagent' (as a matrix in FAB MS) refers to a 5:1 mixture (by weight) of dithiothreitol and dithioerythritol. Microanalyses were obtained using a Perkin Elmer 240 CHN analyzer.

Nuclear magnetic resonance (NMR) spectra were measured on Bruker WP-80 (continuous wave), WH-200, AM-300, WM-360 or WH-400 instruments in the specified solvent with tetramethylsilane (TMS) or deuterated sodium 3-(trimethylsilyl)-1-propanesulfonate (TSP) in D_2O as internal standards in ^1H NMR. For ^{13}C NMR, which were obtained on the WH-400, the deuterated solvent peak was used as the reference. ^{19}F NMR spectra were recorded at 376 MHz using $CDCl_3$ solvent with $CFCl_3$ as an internal standard.

Benzyl Glycinate p-Toluenesulfonate Salt (1).

The literature procedure[137] was followed. A mixture of glycine (38 g, 0.50 mol), p-toluenesulfonic acid (96 g, 0.50 mol) and benzyl alchohol (200 mL, 1.90 mol) in benzene (100 mL) was heated to reflux for 2 h 45 min with azeotropic removal of water. After cooling to room temperature, the mixture was diluted with benzene (500 mL), anhydrous ether (800 mL) was added, and the solution was left overnight at 4 °C. The salt

precipitated as a crystalline solid, 130 g (81%): mp 132-134 °C (lit.[137] mp 132-134 °C); IR (KBr cast) 3400, 2600-3250 (br), 1751, 1253, 1183 cm^{-1}; ^1H NMR (D_2O, 80 MHz) δ 7.0-7.62 (m, 9 H, Ar *H*), 5.1 (s, 2 H, CH_2Ph), 3.77 (s, 2H, CH_2N), 2.18 (s, 3 H, CH_3); FAB MS (glycerol), m/z 338 (MH^+), 166 (M^+, $C_9H_{12}NO_2$).

Benzyl *N*-Benzylglycinate (2).

This ester was required for preparation of **3**. A suspension of benzyl glycinate p-toluenesulfonate salt (**1**) (6.4 g, 20 mmol), benzaldehyde (2.0 mL, 20 mmol), and triethylamine (5.0 mL, 40 mmol) in 10 mL anhydrous methanol was stirred at room temperature for 1 h to produce a clear solution. This was treated with $NaBH_4$ (1.5 g, 40 mmol) in small portions and stirred at 20 °C for 2.5 h. The mixture was poured into 5% $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was dissolved in a minimum amount of CH_2Cl_2. Ether was added, the suspension was filtered, and the filtrate was concentrated *in vacuo* to give 4.96 g of an oil. Flash chromatography[241] (CH_2Cl_2/10% EtOAc) of a portion (1.60 g) gave 0.90 g (74%) **2**: IR ($CHCl_3$ cast) 3063, 3031, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.4 (m, 10 H, Ar *H*), 5.3 (s, 2 H, $ArCH_2O$), 3.8 (s, 2 H, $ArCH_2N$), 3.5 (s, 2 H, CH_2N), 1.9 (br s, 1 H, N*H*); exact mass 255.1256 (255.1259 calcd for $C_{16}H_{17}NO_2$).

Benzyl *N*-Benzyl-*N*-(benzyloxycarbonyl)glycinate (3).

A solution of benzyl *N*-benzylglycinate (**2**) (0.45 g, 1.8 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and triethylamine (0.28 mL, 2.0 mmol) was added. To this was added benzyl chloroformate (0.29 mL, 2.0 mmol). The mixture was stirred at 0 °C for 1.5 h, at 20 °C for 0.5 h, and was then washed with H_2O (5 mL) and 0.5 N HCl (5 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give an oil (0.77 g) which was purified by flash chromatography[241] (CH_2Cl_2) to furnish 0.54 g (69%) of **3**: IR

($CHCl_3$ cast) 1749, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.3 (m, 15 H, Ar *H*), 5.2 (m, 4 H, $COOCH_2Ph$), 4.6 (s, 2 H, NCH_2CO), 4.0 (br d, 2 H, $ArCH_2N$); exact mass 389.1632 (389.1627 calcd for $C_{24}H_{23}NO_4$); Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.03; H, 5.91; N, 3.59. Found: C, 74.28; H, 5.72; N, 3.81.

Benzyl 2-[*N*-Benzyl-*N*-(benzyloxycarbonyl)amino]-3-hydroxypentanoate (4ab).

A solution of **3** (0.39 g, 1.0 mmol) in THF (4 mL) was added dropwise to a cooled (-78 °C) solution of lithium hexamethyldisilazide (from $HN(Si(Me)3)_2$ (0.25 mL, 1.2 mmol), BuLi (1.56 M, 0.77 mL, 1.2 mmol), THF (4 mL), 0 °C). The solution was stirred at -78 °C for 45 min and a solution of propionaldehyde (0.12 mL, 1.7 mmol) in THF (2 mL) was added over 5 min. The resultant colorless solution was stirred at -78 °C for 2.5 h. Water (10 mL) was added and the mixture was acidified (pH 5) with 1N HCl. The aqueous phase was saturated with NaCl and extracted with ether (10 mL) and chloroform (3 x 10 mL). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography[241] (CH_2Cl_2/10% hexane then $CHCl_3$) to give 0.28 g (62%) of **4** as a mixture of diastereomers: IR ($CHCl_3$ cast) 3500 (br), 1737, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.1-7.4 (m, 15 H, Ar H), 3.8-5.3 (m, 9 H), 1.1-1.8 (m, 2 H, CH_2CH_3), 0.9 (m, 3 H, CH_3); MS (CI, NH_3), m/z 448 (MH^+, 100%), 465 ($M{\cdot}NH_4^+$, 15%). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.12. Found: C, 72.39; H, 6.51; N, 3.14.

***N*-Benzyl-4-carbobenzoxy-5-ethyloxazolidin-2-one (5ab).**

A solution of DAST (0.03 mL, 0.25 mmol) in anhydrous CH_2Cl_2 (3 mL) at -78 °C was treated with a solution of **4ab** (0.10 g, 0.22 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at -78 °C for 15 min and gradually brought to room temperature over 1 h at which point 5% $NaHCO_3$ (5 mL) was added. The aqueous phase was extracted with

CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography[241] (CH_2Cl_2/10% hexane) to afford 0.058 g (75%) of **5ab** as an oil (mixture of diastereomers): IR ($CHCl_3$ cast) 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer **a**] δ 7.1-7.4 (m, 10 H, Ar *H*), 5.15 (s, 2 H, C*H*$_2$Ph), 4.9 (d, 1 H, J = 15 Hz, NC*H*$_2$Ph), 4.35-4.4 (m, 1 H, C*H*CH_2CH_3), 4.1 (d, 1 H, J = 15 Hz, NC*H*$_2$Ph), 3.7 (d, 1 H, J = 5 Hz, NC*H*COO), 1.6-1.7 (m, 2 H, C*H*$_2CH_3$), 0.9 (t, 3 H, J = 7.5 Hz, C*H*$_3$); [minor diastereomer **b**] δ 7.1-7.4 (m, 10 H, Ar *H*), 5.2 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 4.9 (d, 1 H, J = 15 Hz, NC*H*$_2$Ph), 4.4-4.5 (m, 1 H, C*H*CH_2CH_3), 4.1 (d, 1 H, J = 15 Hz, NC*H*$_2$Ph), 4.05 (d, 1 H, J = 8.5 Hz, NC*H*COO), 1.45-1.55 (m, 2 H, C*H*$_2CH_3$), 0.96 (t, 3 H, J = 7 Hz, C*H*$_3$); exact mass 339.1479 (339.1470 calcd for $C_{20}H_{21}NO_4$); MS (CI, NH_3), m/z 357 ($M{\cdot}NH_4^+$, 100%); Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.77; H, 6.23; N, 4.12. Found: C, 70.51; H, 6.38; N, 4.06. Similar reaction of compounds **9**, **10** and **11** furnished **5ab** in yields of 58%, 91% and 54%, respectively.

Benzyl *N*-Benzyl-*N*-(methoxycarbonyl)glycinate (6).

Reaction of benzyl *N*-benzylglycinate (**2**) (0.96 g, 3.8 mmol), triethylamine (0.60 mL, 4.0 mmol), and methyl chloroformate (0.30 mL, 4.0 mmol) as described above for **3** gave 1.05 g (89%) of **6**: IR ($CHCl_3$ cast) 1750, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25-7.37 (m, 10 H, Ar*H*), 5.15 (s, 2 H, OC*H*$_2$Ph), 4.60 (s, 2 H, NC*H*$_2$CO), 3.95 (br d, 2 H, NC*H*$_2$Ph), 3.75 (br d, 3 H, C*H*$_3$); exact mass 313.1314 (313.1314 calcd for $C_{18}H_{19}NO_4$). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.46. Found: C, 69.01; H, 6.00; N, 4.47.

Benzyl *N*-Benzyl-*N*-(*tert*-butoxycarbonyl)glycinate (7).

Reaction of benzyl *N*-benzylglycinate (**2**) (0.37 g, 1.4 mmol), triethylamine (0.20 mL, 1.5 mmol), and *tert*-butylpyrocarbonate (0.33 g, 1.5 mmol) as above gave 0.47 g (92%) of **7**: IR ($CHCl_3$ cast) 1751, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25-7.50 (m, 10 H, Ar *H*), 5.15 (s, 2 H, OCH_2Ph), 4.52 (s, 2 H, NCH_2CO), 3.9 (br d, 2 H, NCH_2Ph), 1.45 (br s, 9 H, $C(CH_3)_3$); exact mass 355.1789 (355.1783 calcd for $C_{21}H_{25}NO_4$); MS (CI, NH_3), m/z 373 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.08; N, 3.94. Found: C, 71.24; H, 7.19; N, 3.90.

Benzyl *N*-Benzyl-*N*-(trichloroethoxycarbonyl)glycinate (8).

Reaction of benzyl *N*-benzylglycinate (**2**) (0.37 g, 1.4 mmol), triethylamine (0.20 mL, 1.5 mmol), and trichloroethyl chloroformate (0.20 mL, 0.30 g, 1.5 mmol) as above gave 0.55 g (88%) of **8**: IR ($CHCl_3$ cast) 1751, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25-7.50 (m, 10 H, Ar *H*), 5.18 (s, 2 H, $COOCH_2Ph$), 4.85 (d, 2 H, NCH_2CO), 4.67 (s, 2 H, CH_2CCl_3), 4.05 (d, 2 H, NCH_2Ph); MS (CI, NH_3), m/z 449 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{19}H_{18}NO_4Cl_3$: C, 52.98; H, 4.21; N, 3.25; Cl, 24.69. Found: C, 52.76; H, 4.13; N, 3.19; Cl, 24.75.

Benzyl 2-[*N*-Benzyl-*N*-(methoxycarbonyl)amino]-3-hydroxypentanoate (9ab).

Reaction of **6** (0.31 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and propionaldehyde (0.14 mL, 2.0 mmol) as described for preparation of **4** gave after purification by flash chromatography[241] (CH_2Cl_2/3% EtOAc) 0.23 g (62%) of **9ab** (mixture of diastereomers): IR ($CHCl_3$ cast) 3400, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25-7.50 (m, 10 H, Ar *H*), 5.05 (s, 2 H, $COOCH_2Ph$), 3.5-4.75 (m, 9 H, *CHOH*, NCH_2Ph, $COOCH_2Ph$, $NCOOCH_3$), 1.25-1.75 (m, 2 H, CH_2CH_3), 0.9 (br t, 3 H, CH_3); exact mass 371.1737

(371.1733 calcd for $C_{21}H_{25}NO_5$), MS (CI, NH_3), m/z 372 (MH^+, 100%). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.88; H, 6.79; N, 3.77.

Reaction of **9** with DAST as described for **4** gave **5ab** in 58% yield.

Benzyl 2-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypentanoate (10ab).

Reaction of **7** (0.33 g, 0.90 mmol), $LiN(SiMe_3)_2$ (1.0 mmol), and propionaldehyde (0.09 mL, 1.2 mmol) by the above procedure gave after purification by flash chromatography[241] (CH_2Cl_2/0.1% EtOAc) 0.20 g (55%) of **10ab** (diastereomeric mixture): IR ($CHCl_3$ cast) 3450 (br), 1697 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.0-7.5 (m, 10 H, Ar *H*), 5.0 (s, 2 H, $COOCH_2Ph$), 3.5-4.5 (br m, 5 H, *CHOH*, NCH_2Ph, *NCH*), 1.38 (br s, 9 H, $C(CH_3)_3$), 1.0-1.75 (m, 2 H, CH_2CH_3), 0.88 (br t, 3 H, CH_3); MS (CI, NH_3), m/z 414 (MH^+, 100%). Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.55; N, 3.38. Found: C, 69.60; H, 7.57; N, 3.38.

Reaction of **10** with DAST as described for **4** gave **5ab** in 91% yield.

Benzyl 2-[*N*-Benzyl-*N*-(trichloroethoxycarbonyl)amino]-3 hydroxypentanoate (11ab).

Reaction of **8** (0.30 g, 0.75 mmol), $LiN(SiMe_3)_2$ (0.9 mmol), and propionaldehyde (0.07 mL, 1.0 mmol) by the above procedure gave after purification by flash chromatography[241] (CH_2Cl_2/0.1% EtOAc) 0.2 g (46%) of **11ab** (diastereomeric mixture): IR ($CHCl_3$ cast) 3500 (br), 1720 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.25-7.5 (m, 10 H, Ar *H*), 3.75-5.05 (m, 9 H, CH_2CCl_3, *CHOH*, NCH_2Ph, $NCHCOOCH_2Ph$), 1.25-1.75 (m, 2 H, CH_2CH_3, 0.92 (br t, 3 H, CH_3); exact mass 487.0739 (487.0720 calcd for $C_{22}H_{24}NO_5{}^{35}Cl_3$); MS (CI, NH_3), m/z 505 ($M{\cdot}NH_4^+$).

Reaction of **11** with DAST as described for **4** gave **5ab** in 54% yield.

Ethyl *N*-phthaloylglycinate (12).

A modification of the literature procedure[139] for protection of the amino group was used. A mixture of glycine ethyl ester hydrochloride (28 g, 0.20 mol), phthalic anhydride (30 g, 0.20 mol), and triethylamine (50 mL, 0.36 mol) in toluene (500 mL) was heated to reflux for 5 h with azeotropic removal of water. After cooling to room temperature, the mixture was poured into 10% HCl (350 mL). The aqueous phase was separated and extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a solid that was recrystallized from acetone (90 mL) and hot hexane (~ 250 mL) to give 34 g (73%) of **12**: mp 107-109 °C; IR ($CHCl_3$ cast) 1723, 1419, 1390, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.5-7.9 (m, 4 H, Ar *H*), 4.28 (s, 2 H, NCH_2), 3.7- 4.4 (q, 2 H, J = 7 Hz, CH_2CH_3), 1.25 (t, 3 H, J = 7 Hz, CH_3); exact mass 233.0690 (233.0688 calcd for $C_{12}H_{11}NO_4$). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.00. Found: C, 61.68; H, 4.73; N, 5.78.

4,5-Diphenyl-1,3-dioxol-2-one (13).

The literature procedure[142] was followed. Into a cooled (0-5 °C) 1L three-necked flask equipped with a Dry Ice-acetone condensor, gas inlet tube, pressure equalizing dropping funnel, and magnetic stirrer and charged with a well-stirred suspension of benzoin (106 g, 0.50 mol) in distilled benzene (400 mL), was distilled liquified phosgene (36 mL (-78 °C), 0.53 mol). To the resulting mixture was added dropwise over 1 h N, N-dimethylaniline (64 mL, 0.50 mol). The mixture was allowed to warm to room temperature slowly and stirred for 19 h. After cooling for a short time in an ice bath, the mixture was filtered from N, N-dimethylaniline hydrochloride, and the hydrochloride was washed with benzene (2 x 40 mL). The combined benzene solutions were heated to reflux for 3 h, cooled to room temperature, washed with 0.5 N HCl (3 x 85 mL) and H_2O (3 x 85 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a green syrup. This was dissolved in hot ethanol (200 mL) and left at room temperature overnight. The crystals obtained

(63.7 g) were recrystallized from EtOH (~ 300 mL) to give 54.7 g (46%) of **13**: mp 74-75 °C (lit.[142] mp 75-76 °C); IR ($CHCl_3$ cast) 1820 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.5 (m, Ar *H*); exact mass 238.0533 (238.0629 calcd for $C_{15}H_{10}O_3$).

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)ethanoate (14).

A modification of the literature procedure[142] for protection of the amino group was used. A solution of benzyl glycinate p-toluenesulfonate salt (**1**)[137] (1.9 g, 5.9 mmol), 4,5-diphenyl-1,3-dioxol-2-one (**13**) (1.4 g, 5.9 mmol), DMF (20 mL), and triethylamine (1.0 mL, 7.2 mmol) was stirred 12 h at 20 °C. Ethyl acetate (75 mL) was added and the solution was washed with water (3 x 30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). Combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was dissolved in trifluoroacetic acid (10 mL) and stirred at 20 °C for 2 h. The trifluoroacetic acid was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (60 mL), washed with water (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography[241] (hexane/25% EtOAc) furnished 1.8 g (81%) of **14**: mp 91-93 °C; IR ($CHCl_3$ cast) 1762 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7-7.5 (m, 15 H, Ar *H*), 5.15 (s, 2 H, $COOCH_2Ph$), 4.25 (s, 2 H, NCH_2COO); exact mass 385.1315 (385.1314 calcd for $C_{24}H_{19}NO_4$). Anal. Calcd for $C_{24}H_{19}NO_4$: C, 74.80; H, 4.93; N, 3.63. Found: C, 74.46; H, 4.97; N, 3.61.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-oxobutanoate (15).

To a stirred solution of lithium diisopropylamide (from diisopropylamine (0.2 mL, 1.4 mmol) and BuLi (1.6 M, 0.9 mL, 1.4 mmol)) and TMEDA (0.21 mL, 1.42 mmol) in THF (6 mL) at -78 °C was added dropwise a solution of **14** (385 mg, 1.00 mmol) in THF (4 mL). The resultant yellow solution was stirred at -78 °C for 30 min and a solution of acetic anhydride (0.19 mL, 2.0 mmol) in THF (2 mL) was added The mixture was stirred 2.5 h at -78 °C ,1 h at 0 °C and 1 h at 20 °C. Water (10 mL) was added and the solution

was acidified with 1N HCl to pH ~ 4. Ether (10 mL) was added, the phases were separated and the aqueous phase was extracted with ether (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil that was purified by chromatography on silica (hexane/7.5% EtOAc) to furnish 92 mg (21%) of **15** as a solid: mp 108-110 °C; IR ($CHCl_3$ cast) 1770, 1650, 1380, 1250 cm^{-1} ; ^1H NMR ($CDCl_3$, 80 MHz) δ 12.5 (br s, 1 H, O*H* (enol form)), 7.0-7.5 (m, 1O H Ar *H*), 5.0-5.5 (AB, 2 H, J = 12 Hz, CH_2Ph) 2.05 (s, 3 H, CH_3); exact mass 427.1421 (427.1420 calcd for $C_{26}H_{21}NO_5$). Anal. Calcd for $C_{26}H_{21}NO_5$: C, 73.05; H, 4.95; N, 3.28. Found: C, 73.09; H, 4.73; N, 3.23. (A yield of 23% was obtained using $LiN(SiMe_3)_2$ as the base. TMEDA was not used in this reaction).

Benzyl 2-(4,5-Diphenyl-2-oxo-oxazolin-3-yl)-3-oxopentanoate (16).

The reaction of **14** (385 mg, 1.00 mmol), $LiN(SiMe_3)_2$ (prepared from hexamethyldisilazane (0.63 mL, 3.0 mmol) and BuLi (1.6 M, 1.9 mL, 3.0 mmol)) and propionic anhydride (0.64 mL, 5.0 mmol) as described for the preparation of **15** gave after purification by flash chromatography[241] (hexane/8% EtOAc) 123 mg (28%) of **16** as an oil: IR ($CHCl_3$ cast) 1769, 1650, 1380, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 12.5 (br s, 1 H, O*H* (enol form)), 7.0-7.5 (m, 10 H, Ar *H*) 5.0-5.4 (AB, 2 H, J = 12 Hz,CH_2Ph), 2.0-2.5 (m, 2 H, CH_2CH_3), 1.12 (t, 3 H, CH_3); exact mass 441.1579 (441.1576 calcd for $C_{27}H_{23}NO_5$). Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.06; H, 5.25; N, 3.29.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-oxohexanoate (17).

The reaction of **14** (385 mg, 1.00 mmol), $LiN(SiMe_3)_2$ (prepared from $(Me_3Si)_2$ NH (0.25 mL, 1.2 mmol) and BuLi (1.6 M, 0.8 mL, 1.2 mmol)), and butyric anhydride (0.30 mL, 2.0 mmol) as described for the preparation of **15** gave after purification by flash chromatography[241] (hexane/12% EtOAc) 143 mg (31%) of **17** as an oil: IR ($CHCl_3$ cast)

3400, 1718, 1685, 1450 cm^{-1}; H NMR ($CDCl_3$, 80 MHz) δ 12.55 (br s, 1 H, O*H* (enol form)), 7.0 - 7.5 (m, 5 H, Ar *H*), 5.0 - 5.5 (AB, 2 H, J = 12 Hz, CH_2Ph), 2.0 - 2.5 (m, 2 H, CH_2CO), 1.6 (m, 2 H, CH_2 CH_3), 0.9 (t, 3 H, J = 7 Hz, CH_3); exact mass 455.1736 (455.1733 calcd for $C_{28}H_{25}NO_5$). The compound was light sensitive, and satisfactory elemental analysis could not be obtained.

Procedure for Condensation of Non-functionalized Aldehydes with 14. Preparation of Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxypentanoate (18ab).

$LiN(SiMe_3)_2$ was prepared in dimethyl ether (5 mL) at -78 °C, from $HN(SiMe_3)_2$ (0.25 mL, 1.2 mmol) and BuLi (1.56 M, 0.77 mL, 1.2 mmol) over 30 min. To this was added a solution of **14** (0.39 g, 1.0 mmol) in THF (4 mL) over 5 min. The resulting solution was stirred at -78 °C for 45 min, cooled to -130 °C, and a solution of propionaldehyde (0.14 mL, 2.0 mmol) in THF (2 mL) was added over 5 min. The mixture was stirred at -130 °C for 1.5 h, and a solution of glacial acetic acid (0.07 mL, 1.2 mmol) in THF (1 mL) was added. The mixture was warmed to 20 °C and H_2O (10 mL) was added. The aqueous phase was saturated with NaCl and extracted with ether (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give 0.47 g of an oil. Purification by column chromatography (silica, hexane/10% EtOAc) gave 0.37 g (84%) of **18** as a ca. 5:1 mixture of diastereomers: IR ($CHCl_3$ cast) 3400 (br), 1756, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) [major diastereomer **18a**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.28 (s, 2 H, CH_2Ph), 4.5 (br d, 1 H, O*H*), 4.3-4.4 (m, 1 H, C*H*Et), 4.0 (d, 1 H, J = 5 Hz, NCH_2COO), 1.5-1.7 (m, 2 H, C$H_2$$CH_3$), 0.94 (t, 3 H, C$H_3$); [minor diastereomer **18b**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.2-5.4 (AB, 2 H, J = 12 Hz, CH_2Ph), 5.16 (d, 1 H, J = 5 Hz, O*H*), 4.15-4.22 (m, 1 H, C*H*Et), 4.08 (d, 1 H, J = 4 Hz, NC*H*COO), 1.5-1.8 (m, 2 H, C$H_2$$CH_3$), 0.94 (t, 3 H, C$H_3$); exact mass 443.1737 (443.1733 calcd for

$C_{27}H_{25}NO_5$). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.15. Found: C, 73.07; H, 5.47; N, 3.18.

When the reaction was done at -78 °C a mixture of **18** (70%) and **19** (~ 30%) was obtained. Compound **19** was the only product obtained when the reaction was done at room temperature (see below).

***N*-(1-oxo-1,2-diphenyl-ethyl)-4-carbobenzoxy-5-ethyloxazolidin-2-one (19ab).**

The reaction of **14** (0.39 g, 1.0 mmol) in THF (4mL), $LiN(SiMe_3)_2$ (1.2 mmol, (from $HN(SiMe_3)_2$ (0.25 mL, 1.2 mmol) and BuLi (0.77 mL, 1.56 M, 1.20 mmmol)) in THF (4 mL) and propionaldehyde (0.14 mL, 2.0 mmol) in THF (2 mL) at -100 °C, followed by warming to room temperature gave after work up crude **19**. Recrystallization (EtOAc/hexane) gave 0.39 g (88%) of **19ab**: mp 118-120 °C; IR ($CHCl_3$ cast)1759, 1689, 1405, 1212, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer **19a**] δ 7.18-7.94 (m, 15 H, Ar *H*), 6.64 (apparent d, 1 H, PhC*H*CO), 4.60-4.68 (AB, 2 H, J = 12.5 Hz, COOCH_2Ph), 4.52 (d, 1H, J = 4 Hz, NC*H*COOCH$_2$Ph), 4.24-4.30 (m, 1 H, CH_2CHO), 1.88-2.12 (m, 2 H, CH_2CH_3), 1.04-1.12 (t, 3 H, J = 7 Hz), [minor diastereomer **19b**] δ 7.84-7.94, 7.18-7.52 (m, 15 H, Ar *H*), 6.86 (apparent d, 1 H, PhC*H*CO, 4.76-4.82 (m, 1 H, CH_2CHO), 4.68-4.80 (AB, 2 H, J = 12.5 Hz, COOCH_2Ph), 4.82 (d, 1 H, J = 5.2 Hz, NC*H*COOCH$_2$Ph), 1.34-1.60 (m, 2 H, CH_2CH_3), 0.97 (t, 3 H, J = 6.2 Hz, CH_3); MS (CI, NH_3), m/z 444 (MH^+, 100%), 461 ($M{\cdot}NH_4^+$, 79%). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.15. Found: C, 72.73; H, 5.63; N, 3.17.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanoate (20ab).

Reaction of **14** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and acetaldehyde (0.79 g, 18 mmol) as above gave after purification by flash chromatography[241] (hexane/30% EtOAc) 0.39 g (90%) of **20ab**: IR ($CHCl_3$ cast) 3450 (br), 1758, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer **20a**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.2-5.32 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.7-4.8 (m, 1 H, C*H*OH), 4.32 (br d, 1 H, O*H*), 3.88 (d, 1 H, J = 5.5 Hz, NC*H*COO), 1.25 (d, 3 H, J = 6.5 Hz, CH_3); [minor diastereomer **20b**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.2-5.32 (AB, 2 H, $COOCH_2Ph$), 5.16 (d, 1 H, J = 7 Hz, O*H*), 4.46-4.54 (m, 1 H, C*H*OH), 4.04 (d, 1 H, J = 5 Hz, NC*H*COO), 1.32 (d, 3 H, J = 6.25 Hz, CH_3); exact mass 429.1582 (429.1576 calcd for $C_{26}H_{23}NO_5$). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.72; H, 5.36; N, 3.26. Found: C, 72.73; H, 5.50; N, 3.22.

(2*S*,3*R*) Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanoate (20c).

A modification of the literature[142] procedure was used. L-Threonine (0.59 g, 0.50 mmol) was treated with methanolic tetramethylammonium hydroxide (0.26 mL, 0.50 mmol). The solvent was removed *in vacuo* and the residue was dissolved in anhydrous ethanol. Concentration of this solution gave a solid that was dissolved in DMF (5 mL) and **13** (0.12 g, 0.50 mmol) was added. The mixture was stired 1 h at room temperature, acidified with 2 N HCl to pH ~ 2 and diluted with EtOAc (30 mL). This solution was washed with water (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in trifluoroacetic acid (10 mL) and the solution was stirred 2 h at room temperature. The trifluoroacetic acid was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL). This solution was washed with water (2 x 5 mL), dried (Na_2SO_4) and treated with excess $PhCHN_2$ in CH_2Cl_2. The solution was concentrated *in vacuo* and the

residue was purified by flash chromatography[241] (hexane/30% EtOAc) to give 54 mg (25%) of **20c**: IR ($CHCl_3$ cast) 3100-3600 (br), 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.1-7.6 (m, 15 H, Ar *H*), 5.2-5.3 (AB, 2 H, J = 11 Hz, CH_2Ph), 5.16 (d, 1 H, J =11 Hz, O*H*), 4.52 (m, 1 H, C*H*OH) 4.04 (d, 1 H, J = 4.8 Hz, C*H*N), 1.32 (d, 3 H, J = 6.5 Hz, CH_3); exact mass 429.1575 (429.1577 calcd for $C_{26}H_{23}NO_5$); MS (CI, NH_3), m/z 430 (MH^+, 100%). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.72; H, 5.36; N, 3.26. Found: C, 72.57; H, 5.42; N, 3.22.

(2*S*, 3*S*) Benzyl 2-(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanoate (20d).

This was prepared from L-*allo*-threonine (59 mg, 0.50 mmol), methanolic tetramethylammonium hydroxide (0.26 mL, 0.50 mmol), **13** (119 mg, 0.50 mmol) and $PhCHN_2$ as described for **20c**. The yield was 76 mg (35%): IR ($CHCl_3$ cast) 3500, 1758, 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.1-7.6 (m, 15 H, Ar *H*), 5.2-5.3 (AB, 2 H, J = 12 Hz, CH_2Ph), 4.65 (m, 1 H, C*H*OH), 4.32 (brd, 1 H, O*H*), 3.88 (d, 1 H, J = 5.5 Hz, C*H*N), 1.2 (d, 3 H, J = 6.8 Hz, CH_3); exact mass 429.1575 (429.1577 calcd for $C_{26}H_{23}NO_5$); MS (CI, NH_3), m/z 430 (MH^+, 100%). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.72; H, 5.36; N, 3.26. Found: C, 72.45; H, 5.48; N, 3.14.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxyhexanoate (21ab).

Reaction of **14** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and butyraldehyde (0.10 g, 1.5 mmol) as above gave 0.37 g (80%) of **21**: IR ($CHCl_3$ cast) 3400 (br), 1757, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer **21a**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, $COOCH_2Ph$), 4.38-4.46 (m, 1 H, C*H*OH), 4.43 (br s, 1 H, O*H*), 3.9 (d, 1 H, J = 4.4 Hz, NC*H*COO), 1.2-1.6 (m, 4 H, $CH_2CH_2CH_3$), 0.88 (t, 3 H, CH_3); [minor diastereomer **21b**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, $COOCH_2Ph$), 5.1

(d, 1 H, J = 2 Hz, O*H*), 4.2-4.3 (m, 1 H, C*H*OH), 4.03 (d, 1 H, J = 4.8 Hz, NC*H*COO), 1.2-1.6 (m, 4 H, CH_2CH_2CH$_3$), 0.88 (t, 3 H, CH_3); exact mass 457.1892 (457.1889 calcd for $C_{28}H_{27}NO_5$). Anal. Calcd for $C_{28}H_{27}NO_5$ C, 73.52; H, 5.90; N, 3.06. Found: C, 73.63; H, 5.90; N, 3.06.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-5-methylhexanoate (22ab).

Reaction of **14** (0.39 g, 1.0 mmol), LiN(SiMe$_3$)$_2$ (1.2 mmol), and isovaleraldehyde (0.17 g, 2.0 mmol) as above gave after purification by flash chromatography[214] (hexane/EtOAc/benzene, 74/24/2, v/v) 0.33 g (70%) of **22ab** as a viscous oil: IR ($CHCl_3$ cast) 3500 (br), 1758, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) [major diastereomer **22a**] δ 7.1-7.5 (m, 15 H, Ar *H*), 5.2-5.3 (AB, 2 H, J = 14 Hz, COOCH_2Ph), 4.4 (br d, 1 H, O*H*), 4.15 (m, 1 H, C*H*OH), 3.9 (d, 1 H, J = 5 Hz, NC*H*COO), 1.7-1.85 (m, 1 H, C*H*(CH$_3$)$_2$), 1.5-1.6 (m, 1 H, CH_2), 1.15-1.30 (m, 1 H, CH_2), 0.85-0.95 (d, 6 H, J = 7 Hz, CH_3); visible signals of minor diastereomer [**22b**] δ 5.1-5.3 (AB, 2 H, J = 12 Hz, COOCH_2Ph), 4.0 (d, 1 H, J = 5 Hz, C*H*COO); exact mass 471.2052 (471.2046 calcd for $C_{29}H_{29}NO_5$); MS (CI, NH_3), m/z 472 (MH^+). Anal. Calcd for $C_{29}H_{29}NO_5$ C, 73.88; H, 6.15; N, 2.97. Found: C, 73.68; H, 6.16; N, 2.92.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-4-methylpentanoate (23ab).

Reaction of **14** (0.39 g, 1.0 mmol), LiN(SiMe$_3$)$_2$ (1.2 mmol), and isobutyraldehyde (0.14 g, 2.0 mmol) as above gave after purification by flash chromatography[241] (hexane/EtOAc/benzene, 80/18/2, v/v) 0.37 g (81%) of **23ab**: IR ($CHCl_3$ cast) 3400 (br), 1757, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) [major diastereomer **23a**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.25 (AB, 2 H, J = 12 Hz, COOCH_2Ph), 4.5 (d, 1 H, J = 3 Hz, O*H*), 4.25 (d, 1 H, J = 4.5 Hz, NC*H*COO), 4.0 (m, 1 H, C*H*OH),

1.9-2.0 (m, 1 H, C*H*(CH_3)$_2$), 0.8 (br t, 6 H, (C*H*$_3$)$_2$); [minor diastereomer **23b**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.1-5.4 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 5.3 (br d, 1 H, C*H*), 4.15 (d, 1 H, J = 4.5 Hz, NC*H*COO), 3.7-3.8 (m, 1 H, C*H*OH), 1.8-1.9 (m, 1 H, C*H*(CH_3)$_2$), 1.1 (d, 3 H, J = 6.5 Hz, C*H*$_3$), 0.7 (d, 3 H, J = 6.5 Hz, C*H*$_3$); exact mass 457.1893 (457.1889 calcd for $C_{28}H_{27}NO_5$). Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.52; H, 5.90; N, 3.06. Found: C, 73.64; H, 5.98; N, 2.90.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxy-3-phenylpropanoate (24ab).

Reaction of **14** (0.39 g, 1.0 mmol), LiN($SiMe_3$)$_2$ (1.2 mmol), and benzaldehyde (0.16 g, 1.5 mmol) as above gave after purification by flash chromatography[241] (hexane/EtOAc/benzene, 83/14/7, v/v) 0.33 g (79%) of **24ab**: IR ($CHCl_3$ cast) 3500 (br), 1767 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), [major diastereomer **24a**] δ 7.0-7.5 (m, 20 H, Ar *H*), 5.7 (dd, 1 H, C*H*OH), 5.2-5.4 (AB, 2 H, COOC*H*$_2$Ph), 4.3 (d, 1 H, O*H*), 4.0 (d, 1 H, NC*H*COO); [minor diastereomer **24b**] δ 6.6-6.9 (br m, 20 H, Ar *H*), 6.28 (d, 1 H, O*H*), 5.56 (dd, 1 H, C*H*OH), 5.25 (s, 2 H, COOC*H*$_2$Ph), 4.34 (d, 1 H, NC*H*COO); exact mass 491.1741 (491.1733 calcd for $C_{31}H_{25}NO_5$). Anal. Calcd for $C_{31}H_{25}NO_5$: C, 75.74; H, 5.09; N, 2.85. Found: C, 75.37; H, 5.45; N, 2.76.

3-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-propanoic acid (25).

This was prepared from β-alanine (530 mg, 5.90 mmol) tetramethylammonium hydroxide (5.9 mmol) and 4,5-diphenyl-1, 3-dioxol-2-one (**13**) (1.4 g, 5.9 mmol) as described for **20c** using DMF (15 mL) and trifluroacetic (10 mL). The yield was 1.5 g (82%) mp 163-165 °C; IR ($CHCl_3$ cast) 3500-2700 (br), 1754 cm^{-1}; ^1H NMR ($CDCl_3$/d_6 DMSO (50/1, v/v), 80 MHz) δ 7.25-7.75 (m, 10 H, Ar *H*), 3.75 (t, 2 H, J = 7 Hz, C*H*$_2$CO), 2.25 (t, 2 H, J = 7 Hz, C*H*$_2$N); exact mass 309.0999 (309.0997 calcd for

$C_{18}H_{15}NO_4$). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.51, H, 4.71; N, 4.49.

Bis(triphenylphosphine)copper (I) tetrahydroborate (26).

The literature procedure[143] was followed. To a stirred solution of Ph_3P (10.8 g, 41 mmol) in $CHCl_3$ (75 mL) was added CuCl (2.0 g, 20 mmol) over 5 min. After dissolution of the CuCl (15 min) the yellowish green solution was treated with a suspension of $NaBH_4$ (760 mg, 20.0 mmol) in ethanol (7.5 mL). After stirring 20 min at 20 °C the mixture was poured into water (15 mL). The $CHCl_3$ layer was washed with water (2 x 15 mL), dried ($MgSO_4$) and filtered. Ether (200 mL) was added to the filtrate to precipitate **26** as a white solid which was filtered, washed with ether and dried *in vacuo*. The yield was 10.8 g (90%): mp 169-172 °C (lit.[143] mp 170-174 °C).

Procedures for the preparation of functionalized aldehydes 28, 29, 31 and their precursors.

4,5-Diphenyl-3-(3-hydroxypropyl)-4-oxazolin-2-one (27).

Condensation of 3-aminopropanol (0.442 g, 5.88 mmol) with 4,5-diphenyl-1,3-dioxol-2-one17 (1.40 g) as described above for the preparation of **14** gave a mixture of the protected alcohol and its trifluoroacetate ester. Hydrolysis of this mixture (excess NaOH, aqueous THF, 25 °C, 1 h) gave after recrystallization (EtOAc/Hexane) 1.22 g (70%) of **27**: mp 102-103 °C; IR ($CHCl_3$ cast) 3450 (br), 1754, 1739, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6-7.2 (m, 10 H, Ar *H*), 3.8-3.5 (m, 4 H, NCH_2, OCH_2), 2.8 (br t, 1 H, O*H*), 1.6 (m, 2 H, CH_2); exact mass 295.1205 (295.1209 calcd for $C_{18}H_{17}NO_3$). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.74. Found: C, 72.98; H, 5.64; N, 4.85.

4,5-Diphenyl-3-(3-oxopropyl)-4-oxazolin-2-one (28).

This material was obtained by oxidation of **27** using the Swern procedure. A solution of oxalyl chloride (0.2 mL, 2.2 mmol) in anhydrous CH_2Cl_2 (4 mL) was cooled to -78 °C and DMSO (0.30 mL, 4.4 mmol) in CH_2Cl_2 (1 mL) was added slowly. The mixture was stirred at -78 °C for 2 min and a solution of the alcohol (0.53 g, 1.8 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The resulting mixture was stirred at -78 °C for 30 min and triethylamine (1.4 mL, 1.0 g, 10 mmol) was added. The mixture was stirred at -78 °C for 5 min and brought to 20 °C. Water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic phases were dried (Na_2SO_4) and concentrated to give 0.64 g of an oil which was purified by flash chromatography[241] (CH_2Cl_2/10% EtOAc) to afford 0.47 g (89%) of **28**: mp 102-103 °C; IR ($CHCl_3$ cast) 1775 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.13 (s, 1 H, C*H*O), 7.1-7.6 (m, 10 H, Ar *H*), 3.8 (t, 2 H, J = 7 Hz, NCH_2CH$_2$), 2.77 (t, 2 H, J = 7 Hz, CH_2CHO); exact mass 293.1051 (293.1052 calcd for $C_{18}H_{15}NO_3$). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.50; H, 4.98; N, 4.64.

4,5-Diphenyl-3-(4-oxobutyl)-4-oxazolin-2-one (29).

This was prepared from commercially available 4-aminobutyraldehyde diethyl acetal (1.0 mL, 0.94 g, 5.9 mmol), 4,5-diphenyl-1,3-dioxol-2-one (**13**) (1.4 g, 5.9 mmol), and triethylamine (1.0 mL, 0.7 g, 7.2 mmol). The residue obtained after the CF_3COOH step[142] was dissolved in THF/H_2O (3:1 v/v, 20 mL). The solution was stirred 20 min at 20 °C and the THF was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water and brine. Drying (Na_2SO_4) and concentration gave 2.30 g of an oil which was recrystallized from EtOAc/hexane to give 1.17 g (65%) of **29**: mp 64-66 °C; IR ($CHCl_3$ cast) 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.6 (s, 1 H, C*H*O), 7.0-8.0 (m, 10 H, Ar *H*), 3.55 (t, 2 H, J = 7 Hz, CH_2N), 2.47 (t, 2 H, J = 7 Hz, CH_2CHO), 1.53 (m, 2

H, $CH_2CH_2CH_2$); exact mass 307.1218 (307.1209 calcd for $C_{19}H_{17}NO_3$). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.80; N, 4.56. Found: C, 73.99; H, 5.80; N, 4.40.

(*E*)-Dibenzyl 2-Butendioate (30).[146,147]

To a stirred solution of fumaryl chloride (10.8 mL, 0.10 mol) in THF (20 mL at 0 °C) was added a solution of benzyl alchohol (20.6 mL) in THF (10 mL). The mixture was stirred at 0 °C for 10 min then 1 h at 20 °C and 30 min at 55 °C. Solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed successively with water, aqueous sodium bicarbonate (5%) and brine. Drying (Na_2SO_4) and concentration *in vacuo* gave a solid that was recrystallized from hexane (350 mL) to give 26 g (88%) of **30**: mp 56-58 °C (lit.[146] mp 58.5-59.5 °C); IR ($CHCl_3$ cast) 1709, 1293, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.38 (br s, 10 H, Ar *H*), 6.9 (s, 2 H, C*H*=C*H*), 5.25 (s, 4 H, CH_2Ph), exact mass 296.1046 (296.1048 calcd for $C_{18}H_{16}O_4$).

Benzyl 2-Oxoethanoate (31).[148]

The literature procedure[148] was used. Ozone was bubbled through a stirred solution of **30** (10 g, 33 mmol) in CH_2Cl_2 (10 mL) at -78 °C till the solution was blue. Excess ozone was then removed by bubbling argon through the solution, dimethyl sulphide (5.0 mL, 67 mmol) was added and the mixture was stirred 1 h at -78 °C and overnight at 20 °C. The solvent was removed *in vacuo* and the residue was vacuum distilled to give **31** as a viscous liquid, 6.48 g (60%): bp 105-108 °C/4.5 mm; IR ($CHCl_3$ cast) 1759, 1284, 1216, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.4 (s, 1 H, *CH*O), 7.0-7.5 (m, 5 H, Ar *H*), 5.32 (s, 2 H, CH_2Ph); exact mass 164.0472 (164.0472 calcd for $C_9H_8O_3$). This material polymerizes slowly. Depolymerization can be effected by heating, and the material was always purified by bulb to bulb distillation before use.

Condensation of Functionalized Aldehydes with 14

Benzyl 2,5-Bis(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxypentanoate (32ab).

To a solution of $LiN(SiMe_3)_2$ ((0.6 mmol), prepared from hexamethyldisilazane (0.13 mL, 0.60 mmol) and BuLi (0.43 mL, 1.4 M, 0.60 mmol)) in THF (2 mL) was added a solution of **14** in THF (4 mL). The mixture was stirred at -78 °C for 35 min and a solution of the aldehyde **28** (0.15 g, 0.5 mmol) in THF (4 mL) was added. The mixture was stirred at -78 °C for 3 h and quenched with acetic acid (0.1 mL, 1.7 mmol) in THF (0.8 mL). Water (5 mL) was added. The aqueous phase was saturated with NaCl and extracted with ether (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography[241] (hexane/EtOAc/benzene, 60/36/4, v/v) to give 0.20 g (60%) of **32ab**: IR ($CHCl_3$ cast) 3500 (br), 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) [major diastereomer **32a**] δ 7.1-7.5 (m, 25 H, Ar *H*), 5.1-5.25 (AB, 2 H, J = 12 Hz, $COOCH_2Ph$), 4.4 (br s, 1 H, O*H*), 4.2-4.3 (m, 1 H, C*H*OH), 3.94 (d, 1 H, J = 4.5 Hz, NC*H*COO), 3.62 (t, 2 H, J = 7 Hz, CH_2N), 1.7-1.9 (m, 2 H, CH_2); [minor diastereomer **32b**] δ 7.1-7.5 (m, 25 H, Ar *H*), 5.1-5.25 (AB, 2 H, $COOCH_2Ph$), 5.0 (d, 1 H, O*H*), 4.16-4.24 (m, 1 H, C*H*OH), 4.02 (d, 1 H, J = 6.5 Hz, NC*H*COO), 3.62 (br t, 2 H, CH_2N), 0.8 to 1.4 (m, 2 H, CH_2); FAB MS (Cleland's reagent), m/z 679.46 (MH^+, 50.5%). Anal. Calcd for $C_{42}H_{34}N_2O_7$: C, 74.33; H, 5.01; N, 4.12. Found: C, 73.94; H, 5.22; N, 3.99.

Benzyl 2,6-Bis(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxyhexanoate (33ab).

Reaction of **14** (0.19 g, 0.5 mmol), $LiN(SiMe_3)_2$ (0.6 mmol), and aldehyde **29** (0.15 g, 0.5 mmol) at -78 °C for 4 h gave after purification by flash chromatography[241] (as above) 0.19 g (55%) of **33**: IR ($CHCl_3$ cast) 3500 (br), 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) [major diastereomer **33a**] δ 7.0-7.6 (m, 25 H, Ar *H*), 5.22 (AB, 2 H, J = 12.5 Hz,

COOC*H*$_2$Ph), 4.38 (br s, 1 H, O*H*), 4.22-4.32 (m, 1 H, C*H*OH), 3.87 (d, 1 H, J = 5 Hz, NC*H*COO), 3.4-3.64 (m, 2 H, C*H*$_2$N), 1.36-1.8 (m, 4 H, C*H*$_2$); [minor diastereomer **33b**] δ 7.0-7.6 (m, 25 H, Ar *H*), 5.22 (AB, 2 H, J = 12.5 Hz, COOC*H*$_2$Ph), 5.06 (d, 1 H, O*H*), 4.1-4.2 (m, 1 H, C*H*OH), 4.0 (d, 1 H, J = 5 Hz, NC*H*COO), 3.4-3.64 (m, 2 H, C*H*$_2$N), 1.36-1.8 (m, 4 H, C*H*$_2$). FAB MS (Cleland's reagent), m/z 693.73 (MH^+, 100%). Anal. Calcd for $C_{43}H_{36}N_2O_7$: C, 74.56; H, 5.20; N, 4.04. Found: 74.35; H, 5.30; N, 4.10.

Dibenzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-hydroxybutanedioate (34ab).

Reaction of **14** (0.39 g, 1.0 mmol), $LiN(SiMe_3)_2$ (1.2 mmol), and benzyl glyoxylate (**31**) (0.24 g, 1.5 mmol) at -78 °C for 3 h gave 0.30 g (55%) of a mixture of diastereomers which were separable by chromatography on silica (hexane/10% EtOAc). Major diastereomer **34a** (61%): IR ($CHCl_3$ cast) 3200-3450 (br), 1758, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.9-7.5 (m, 20 H, Ar *H*), 6.22 (d, 1 H, J = 12 Hz, O*H*), 5.16-5.3 (2 x AB, 4 H, J = 12 Hz each, COOC*H*$_2$Ph), 4.98 (dd, 1 H, J = 12, 5 Hz, C*H*OH), 4.6 (d, 1 H, J = 5 Hz, NC*H*COO); exact mass 549.1784 (549.1788 calcd for $C_{33}H_{27}NO_7$); MS (CI, NH_3) 550 (MH^+, 100%). Anal. Calcd for $C_{33}H_{27}NO_7$: C, 72.13; H, 4.91; N, 2.55. Found: C, 71.91; H, 4.98; N, 2.40.

Minor diastereomer **34b** (39%): IR ($CHCl_3$ cast) 3200-3450 (br), 1761, 1756 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.[illegible]-7.6 (m, 20 H, Ar *H*), 5.0-5.2 (2 x AB, 4 H, J = 12.5, 12 Hz, COOC*H*$_2$Ph), 4.92 (t, [illegible] H, J = 3.5 Hz, C*H*OH), 4.78 (d, 1 H, J = 3 Hz, NC*H*COO): exact mass 549.1773 (549.1788 calcd for $C_{33}H_{27}NO_7$). Anal. Calcd for $C_{33}H_{27}NO_7$: C, 72.13; H, 4.91; N, 2.55. Found: C, 71.95; H, 5.18; N, 2.61.

Phenyldiazomethane (35).

The literature procedure[149] was followed. Benzaldehyde (20 mL, 0.20 mol) was added slowly to hydrazine hydrate (19 mL, 0.40 mol) at 5 °C. The temperature was allowed to rise to 30 °C, the mixture was stirred 1 h at this temperature and then extracted with ether (3 x 20 mL). The solvent was removed *in vacuo* and the residue was distilled to give benzaldehyde hydrazone, 14.3 g (0.12 mol): bp105-107 °C/4 mm. The liquid hydrazone was dissolved in CH_2Cl_2 (300 mL) and $MgSO_4$ (12 g, 0.10 mol) was added. The mixture was stirred with cooling (ice-water) and MnO_2 (48 g, 0.55 mol) was added over 20 min. The mixture was filtered from the salts, the salts were washed with CH_2Cl_2 till colourless, and the combined bright red CH_2Cl_2 solutions were cooled to -35 °C for 30 min and filtered. The solution thus obtained was stored at -20 °C and used when required.

Procedure for Fluorination of Protected β-Hydroxy α-Amino Acid Esters 18ab, 20ab, 21ab and 22ab with DAST. Preparation of Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluoropentanoate (36ab).

A solution of DAST (0.11 mL, 0.15 g, 0.9 mmol) in CH_2Cl_2 (12 mL) was cooled to -78 °C and a solution of **18** (0.37 g, 0.80 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h, at -45 °C for 2 h, and was then gradually brought to 20 °C. Water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The organic phases were dried (Na_2SO_4) and concentrated to give 0.34 g of an oil which was purified by chromatography (SiO_2, hexane/8% EtOAc) to give 0.22 g (48%) of **36** and 0.06 g (17%) of **37**. For **36** (nearly equal mixture of diastereomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz), [major isomer **36a**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.2 (AB, 2 H, J = 6 Hz, C*H*$_2$Ph), 5.1-5.4 (m, 1 H, FC*H*), 4.26 (br t, 1 H, J = 8.8 Hz, NC*H*COO), 1.5-1.68 (m, 2 H, C*H*$_2$CH$_3$), 0.92 (t, 3 H, J = 8.1 Hz, C*H*$_3$); [minor isomer **36b**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.24 (AB, 2 H, J = 6.2 Hz, C*H*$_2$Ph), 5.1-5.4 (m, 1 H, FC*H*), 4.2 (dd, 1 H, J = 13.6, 6.8 Hz, NC*H*COO),

1.7-2.05 (m, 2 H, CH_2CH_3), 0.98 (t, 3 H, J = 7.2 Hz, CH_3); exact mass 445.1686 (445.1689 calcd for $C_{27}H_{24}NO_4F$); MS (CI, NH_3), m/z 463 ($M{\cdot}NH_4^+$, 100%). ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ std) δ -187.1 to -187.4 (m) and -189.5 to -189.8 (m). The compound was light sensitive and a satisfactory analysis could not be obtained.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-2-pentenoate (37ab). (mixture of isomers): IR ($CHCl_3$ cast) 1768, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major isomer **37a**] δ 7.2-7.4 (m, 15 H, Ar *H*), 7.1 (t, 1 H, J = 7 Hz, $CHCH_2$), 5.1 (AB, 2 H, CH_2Ph), 2.0-2.4 (m, 2 H, CH_2CH_3), 1.0 (t, 3 H, J = 6 Hz, CH_3); [minor isomer **37b**] δ 7.2-7.4 (m, 15 H, Ar *H*), 6.3 (t, 1 H, J = 7 Hz, $CHCH_3$), 5.1 (AB, 2 H, CH_2Ph), 2.6 (m, 2 H, CH_2CH_3), 0.95 (t, 3 H, J = 6 Hz, CH_3); exact mass 425.1623 (425.1627 calcd for $C_{27}H_{23}NO_4$), MS (CI, NH_3) m/z 443 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.21; H, 5.44; N, 3.29. Found: C, 76.25; H, 5.40; N, 3.28.

A similar reaction of **18** with **38** (below) instead of DAST produced **37** in 80% yield.

Bis(diethylamino)sulfur difluoride (38).

This was prepared by the literature procedure.[58] To a stirred solution (diethylamino)sulfur trifluoride (1.2 mL, 10 mmol) in $CFCl_3$ (10 mL) at -78 °C was added trimethylsilyl diethylamine (1.0 mL, 10 mmol) over 5 min. The solution was stirred 15 min at -78 °C, warmed to 20 °C and filtered under an atmosphere of argon. Evaporation of solvent under a stream of argon gave a yellow oil which was stored under argon at 0 °C and used further.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluorobutanoate (39ab).

The procedure described for the preparation of **37** was used to convert **20** (0.30 g, 0.7 mmol) with DAST (0.16 mL, 0.20 g, 1.3 mmol) to give after purification by MPLC

(hexane/25% EtOAc) 0.14 g (45%) of **39** and 0.070 g (24%) of **40**. For **39** (nearly equal mixture of diastereomers): IR ($CHCl_3$ cast) 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), [major isomer **39a**] δ 7.18-7.58 (m, 15 H, Ar *H*), 5.38-5.46 (m, 1 H, C*H*F), 5.16-5.28 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 4.18-4.26 (dd, 1 H, J_{H-F} = 14 Hz, J_{H-H} = 6.5 Hz, NC*H*COO), 1.4-1.54 (dd, 3 H, J_{H-F} = 12.5 Hz, J_{H-H} = 6 Hz, C*H*$_3$); [minor isomer **39b**] δ 7.18-7.58 (m, 15 H, Ar *H*), 5.5-5.6 (m, 1 H, C*H*F), 5.16-5.28 (AB, 2 H, COOC*H*$_2$Ph), 4.16 (br t, 1 H, J = 8.5 Hz, NC*H*COO), 1.4-1.54 (dd, 3 H, J_{H-F} = 13.5 Hz, J_{H-H} = 6 Hz, C*H*$_3$), exact mass 431.1530 (431.1533 calcd for $C_{26}H_{22}NO_2F$). Anal. Calcd for $C_{26}H_{22}NO_2F$: C, 72.38; H, 5.10; N, 3.25. Found: C, 72.14; H, 5.07; N, 3.28. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ std) δ -175.9 to -176.3 (m), -178.3 to -178.6 (m).

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-2-butenoate (40ab). (mixture of isomers): IR ($CHCl_3$ cast) 1768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), [major isomer **40a**] δ 7.1-7.5 (m, 16 H, Ar *H* and C*H*CH$_3$), 5.1 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 1.88 (d, 3 H, J = 7 Hz, C*H*$_3$); [minor isomer **40b**] 7.1-7.5 (m, Ar *H*), 6.5 (q, 1 H, J = 7 Hz, C*H* CH$_3$), 5.1 (s, 2 H, COOC*H*$_2$Ph), 2.12 (d, 3 H, J = 7 Hz, C*H*$_3$); exact mass 411.1466 (411.1466 calcd for $C_{26}H_{22}NO_4$). Anal. Calcd for $C_{26}H_{22}NO_4$: C, 75.88; H, 5.11; N, 3.40. Found: C, 75.76; H, 5.32; N, 3.39.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluorohexanoate (41ab).

Reaction of **21** (0.33 g, 0.70 mmol) and DAST (0.1 mL, 0.13 g, 0.80 mmol) as above gave after purification by flash chromatography[241] (hexane/EtOAc/benzene, 70/28/2, v/v) 0.22 g (65%) of **41** (nearly equal mixture of diastereomers): IR ($CHCl_3$ cast) 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), [major isomer **41a**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.1-5.3 (m, 1 H, C*H*F), 5.2-5.3 (AB, 2 H, J = 11.5 Hz), 4.2-4.3 (dd, 1 H, J_{H-F} = 13 Hz, J_{H-H} = 6 Hz, NC*H*COO), 1.4-1.7 (m, 4 H, C*H*$_2$), 0.92-1.0 (t, 3 H, C*H*$_3$); [minor isomer **41b**] δ 7.2-7.6 (m, 15 H, Ar *H*), 5.4-5.5 (m, 1 H, C*H*F), 5.2-5.3 (AB, 2 H,

COOC*H*$_2$Ph), 4.2-4.25 (br t, 1 H, J = 3 Hz, NC*H*COO), 1.7-2.0 (m, 4 H, C*H*$_2$), 0.85-0.92 (t, 3 H, C*H*$_3$); exact mass 459.1852 (459.1846 calcd for $C_{28}H_{26}NO_4F$). Anal. Calcd for $C_{28}H_{26}NO_4F$: C, 73.20; H, 5.66; N, 3.05. Found: C, 72.95; H, 5.76; N, 2.97. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ std) δ -186.3 to -186.6 (m), and -188.5 to -188.8 (m).

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-2-hexenoate (42ab)

This was isolated from a similar reaction of **21** (0.16 g, 0.4 mmole) and DAST (0.05 mL, 0.07 g, 0.4 mmol). The yield after purification by flash chromatography[241] (hexane/EtOAc/benzene, 70/6/24, v/v) was 0.02 g (13%) (mixture of isomers): IR ($CHCl_3$ cast) 1767 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); [major isomer **42a**] δ 7.15-7.6 (m, 15 H, Ar*H*), 7.1-7.15 (t, 1 H, C*H*CH$_2$), 5.14 (s, 2 H, COOC*H*$_2$Ph), 2.0-2.4 (m, 2 H, C*H*$_2$), 1.2-1.6 (m, 2 H, C*H*$_2$), 0.85-1.0 (t, 3 H, C*H*$_3$); [minor isomer **42b**] δ 7.1-7.6 (m, Ar*H*), 6.3-6.4 (t, 1 H, C*H*CH$_2$), 5.2 (AB, 2 H, COOC*H*$_2$Ph), 2.4-2.7 (m, 2 H, C*H*$_2$), 1.2-1.6 (m, 2 H, C*H*$_2$), 0.8 (t, 3 H, C*H*$_3$); exact mass 439.1777 (439.1770 calcd for $C_{28}H_{25}NO_4$). Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.53; H, 5.69; N, 3.18. Found: C, 76.31; H, 5.77; N, 2.99.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-3-fluoro-5-methylhexanoate (43ab).

Reaction of **22** (0.33 g, 0.7 mmol) and DAST (0.15 mL, 0.20 g, 1.7 mmol) as above gave after purification by MPLC (hexane/EtOAc/benzene, 82/14/4, v/v) 0.21 g (65%) of **43** and 0.04 g (12%) of **44**. For **43** (nearly equal mixture of diastereomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz); [major isomer **43a**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.2-5.3 (m, 1 H, C*H*F), 4.2-4.28 (1 H, dd, $J_{H\text{-}F}$ = 13 Hz, $J_{H\text{-}H}$ = 9 Hz, NC*H*COO), 5.1-5.3 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 1.4-1.8 (m, 3 H, C*H*$_2$CH), 0.93 (d, 3 H, J = 6 Hz, C*H*$_3$), 0.95 (d, 3 H, J = 6 Hz, C*H*$_3$); [minor isomer **43b**] δ 7.1-7.6 (m, 15 H, Ar *H*), 5.38-5.44 (m, 1 H, C*H*F), 5.18-5.22 (AB, 2 H, J = 12 Hz,

COOCH_2Ph), 4.16-4.22 (t, 1 H, J = 8.5 Hz, NCHCOO), 1.4-1.8 (m, 3 H, CH_2CH), 0.88 (t, 6 H, J = 6.5 Hz, CH_3); exact mass 473.1990 (473.2002 calcd for $C_{29}H_{28}NO_4F$). Anal. Calcd for $C_{29}H_{28}NO_4F$: C, 73.57; H, 5.91; N, 2.95. Found: C, 73.76; H, 5.97; N, 2.85. ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$ std) δ -184.8 to -185.1 (m), and -186.7 to -187.0 (m).

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-5-methyl-2-hexenoate (44ab).

(mixture of isomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); [major isomer **44a**] δ 7.15-7.5 (m, 16 H, Ar *H* and CHCH$_2$), 5.1 (AB, 2 H, J = 13 Hz, COOCH_2Ph), 2.0-2.3 (m, 2 H, CH_2), 1.7-1.8 (m, 1 H, CH(CH$_3$)$_2$), 0.95 (d, 3 H, J = 6.5 Hz, CH_3), 0.85 (d, 3 H, J = 6.5 Hz, CH_3); [minor isomer **44b**]: δ 7.15-7.5 (m, Ar *H*), 6.4 (t, 1 H, J = 8 Hz, CHCH$_2$), 5.1-5.2 (AB, 2 H, J = 11 Hz, COOCH_2Ph), 2.5 (t, 2 H, J = 8 Hz, CH_2), 1.5-1.65 (m, 1 H, CH(CH$_3$)$_2$), 0.75 (d, 6 H, J = 6.5 Hz, CH_3); exact mass 453.1947 (453.1940 calcd for $C_{29}H_{27}NO_4$). Anal. Calcd for $C_{29}H_{27}NO_4$: C, 76.78; H, 6.00; N, 3.09. Found: C, 76.39; H, 5.89; N, 2.97.

Dehydration of Protected β-Hydroxy α-Amino Acid Esters by DAST.

Attempted fluorination of **23**, **32**, **33** and **34** by the procedure described above gave none of the desired fluoro compound but afforded **45**, **46**, **47**, and **48** respectively, as the major products.

Benzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)-4-methyl-2-pentenoate (45).

This was obtained from the reaction of **23** (0.11 g, 0.34 mmol) with DAST (0.05 mL, 0.07 g, 0.4 mmol) and TASF (0.24 g, 0.9 mmol). The yield after purification by flash chromatography[241] (hexane/EtOAc/benzene, 84/14/2, v/v) was 0.06 g (54%, 75% based

on recovered starting material): IR ($CHCl_3$ cast) 1768, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 7.1-7.5 (m, 15 H, Ar *H*), 6.98 (d, 1 H, J = 11 Hz, C*H*CH$(CH_3)_2$), 5.2 (s, 2 H, COOC*H*$_2$Ph), 2.65 (m, 1 H, C*H*$(CH_3)_2$), 1.16 (d, 3 H, J = 7 Hz, C*H*$_3$), 0.82 (d, 3 H, J = 7 Hz, C*H*$_3$); exact mass 439.1778 (439.1783 calcd for $C_{28}H_{25}NO_4$). Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.53; H, 5.69; N, 3.18. Found: C, 76.60; H, 5.84; N, 3.31.

Benzyl 2,5-Bis(4,5-diphenyl-2-oxo-4-oxazolin-3-yl)-2-pentenoate (46ab).

This was obtained from the reaction of **32** (0.14 g, 0.2 mmol) and DAST (0.04 mL, 0.05 g, 0.3 mmol). The yield after purification by flash chromatography[241] (CH_2Cl_2/6% EtOAc) was 34 mg (25%, 46% based on recovered starting material), (mixture of diastereomers): IR ($CHCl_3$ cast) 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): [major isomer **46a**] δ 7.1-7.5 (m, 25 H, Ar *H*), 7.1 (m, 1 H, C*H*CH_2), 5.1 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 3.65 (m, 2 H, C*H*$_2$N), 2.5 (m, 2 H, CHC*H*$_2$); [minor isomer **46b**] δ 7.1-7.5 (m, Ar *H*), 6.9 (t, 1 H, J = 6 Hz, C*H*CH_2), 5.04 (s, 2 H, COOC*H*$_2$Ph), 3.65 (m, 2 H, C*H*$_2$N), 2.5 (m, 2 H, CHC*H*$_2$); FAB MS (Cleland's reagent), m/z 661 (MH^+, 100%), 660 (M^+, 40%). The compound was light sensitive and satisfactory elemental analysis could not be obtained.

A similar reaction of **32** with DAST in $CFCl_3$ gave **46** in 45% yield.

Benzyl 2,5-Bis(4,5-diphenyl-2-oxo-4-oxazolyn-3-yl)-2-hexenoate (47a,b).

This was obtained from the reaction of **33** (0.090 g, 0.14 mmol) and DAST (0.020 mL, 0.030 g, 0.2 mmol). The yield after purification by flash chromatography[241] (CH_2Cl_2/4% EtOAc) was 0.050 g (56%, 73% based on recovery of starting material), (mixture of diastereomers): IR ($CHCl_3$ cast) 1763 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): [major isomer **47a**] δ 7.1-7.6 (m, 25 H, Ar *H*), 6.9 (t, 1 H, J = 7 Hz, C*H*CH_2), 5.1 (AB, 2 H, J = 12 Hz, COOC*H*$_2$Ph), 3.5 (t, 2 H, J = 6 Hz, C*H*$_2$N), 1.9-2.3 (m, 2 H, CHC*H*$_2$), 1.4-1.7 (m, 2 H, C*H*$_2$$CH_2$N); [minor isomer **47b**] δ 7.1-7.6 (m, 25 H, Ar *H*), 6.15 (t, 1

H, C*H*CH_2), 5.04 (s, 2 H, COOC*H*$_2$Ph), 3.3-3.4 (t, 2 H, C*H*$_2$N), 1.9-2.3 (m, 2 H, CHC*H*$_2$), 1.2-1.4 (m, 2 H, C*H*$_2$$CH_2$N); exact mass 674.2409 (674.2416 calcd for $C_{43}H_{34}N_2O_6$). Anal. Calcd for $C_{43}H_{34}N_2O_6$: C, 76.55; H, 5.04; N, 4.15. Found: C, 76.63; H, 5.21; N, 4.07.

Dibenzyl 2-(4,5-Diphenyl-2-oxo-4-oxazolyn-3-yl)-2-butendioate (48ab).

This was obtained from **34** (0.32 g, 0.6 mmol of pure major diastereomer) and DAST (0.12 mL, 0.16 g, 1.0 mmol). Purification by flash chromatography[241] (hexane/25% EtOAc) gave 0.2 g (76%) of **48**, (mixture of diastereomers): IR ($CHCl_3$ cast) 1773, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): [major isomer **48a**] δ 7.1-7.4 (m, 20 H, Ar*H*), 7.05 (s, 1 H, C*H*COO), 5.2 (s, 2 H, COOC*H*$_2$Ph), 5.05 (br d, 2 H, J = 6 Hz, COOC*H*$_2$Ph); [minor isomer **48b**] δ 7.1-7.4 (m, Ar *H*), 6.2 (s, 1 H, C*H*COO), 5.0 (s, 2 H, COOC*H*$_2$ Ph), 4.8 (s, 2 H, COOC*H*$_2$Ph); exact mass 531.1669 (531.1682 calcd for $C_{33}H_{25}NO_6$). Anal. Calcd for $C_{33}H_{25}NO_6$: C, 74.57; H, 4.70; N, 2.63. Found: C, 74.52; H, 4.71; N, 2.65.

2-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)ethanoic Acid (49).

The literature procedure[142] was used. Glycine (1.88 g, 25.0 mmol) was dissolved in methanolic tetramethylammonium hydroxide (25 mmol) and the solvent was removed *in vacuo*. The residue was dissolved in DMF (20 mL) and to the stirred solution was added 4, 5-diphenyl-1,3-dioxol-2-one (**13**) (5.95 g, 25.0 mmol). The solution was stirred 30 min at 20 °C, acidified with 2N HCl, diluted with EtOAc (70 mL). Phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (3 x 25 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil. This was dissolved in trifluroacetic acid (20 mL) and stirred 2 h at 20 °C. The trifluroacetic acid was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (3 x 15 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil.

Recrystallization from EtOAc/hexane gave 4.86 g (66%) of **49**: mp 179-181 °C; IR ($CHCl_3$ cast) 3400-2300 (br), 1763, 1710, 1450, 1390, 1240 cm^{-1}; ^1H NMR ($CDCl_3/d_6$ DMSO (50/1, v/v), 80MHz, d_6 DMSO) δ 10.8 (br s, 1 H, COO*H*), 7.0-7.75 (m, 10 H, Ar *H*), 4.15 (s, 2 H, CH_2); exact mass 295.0854 (295.0854 calcd for $C_{17}H_{13}NO_4$). Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.01; H, 4.52; N, 4.71.

(*R*)-3-(1-Oxo-2-[4,5-Diphenyl-2-oxo-4-oxazolin-3-yl]ethyl)-4-benzyloxazolidin-2-one (50).

To a stirred solution of **49** (295 mg, 1.00 mmol) in THF (15 mL) at 0 °C was added BuLi (1.4M, 0.7 mL, 1.0 mmol). To the resulting yellow suspension was added pivaloyl chloride (0.12 mL, 1.00 mmol) and the mixture was stirred 1.5 h at 0 °C. A suspension of the lithium salt of (*S*)-4-benzyloxazolidin-2-one (from (*S*)-4-benzyloxazolidin-2-one (177 mg, 1.00 mmol) and BuLi (1.4 M, 0.7 mL, 1.0 mmol)) in THF (5 mL) was added. The resulting bright orange suspension was stirred 1 h at 0 °C, and water (10 mL) was added. The phases were separated, the aqueous phase was saturated with NaCl and extracted with ether (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give an oil that was purified by flash chromatography[241] (hexane/40% EtOAc) to give 114 mg (25%) of **50**: mp 89-91 °C (softens at 80 °C); IR ($CHCl_3$ cast) 1763, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.0-7.6 (m, 5 H, Ar *H*), 4.7-4.9 (AB, 2H, J = 16 Hz, CH_2CO), 4.6-4.7 (m, 1 H, C*H*), 4.16-4.23 (m, 2 H, CH_2O), 3.1 (dd, 1 H, J = 3, 14 Hz, CH_2Ph), 2.8 (dd, 1 H, J = 8, 14 Hz, CH_2Ph); exact mass 454.1533 (454.1529 calcd for $C_{27}H_{22}N_2O_5$). Anal. Calcd for $C_{27}H_{22}N_2O_5$: C, 71.36; H, 4.84; N, 6.16. Found: C, 71.12; H, 5.09; N, 5.86.

Deprotection of 36, 39, 41 and 43 to β-Fluoro α-Amino Acids 51-54.

Preparation of 2-Amino-3-fluoropentanoic Acid (β-fluoro norvaline) (51ab).

A mixture of 10% palladium on charcoal (0.10 g) and **36** (0.27 g, 0.60 mmol) in 25 mL ethanol was hydrogenated for 2 days in a low pressure hydrogenation apparatus at 45 psi until no fluorescent material was seen by thin layer chromatography. The mixture was filtered through Celite, the Celite was washed with ethanol, and the filtrate was concentrated *in vacuo*. The residue was treated with water (10 mL) and filtered. Concentration and lyophilization of the filtrate gave 0.12 g of solid which was purified by ion exchange chromatography (AG50 x 8, H^+ form) to give 0.070 g (88%) of **51**, as a nearly equal mixture of diastereomers: mp 189-191 °C (lit.[30] mp 182 °C (dec)); IR (KBr) 2600-3200 (br), 1588 cm^{-1}; ^1H NMR (D_2O, 300 MHz): isomer **51a**: δ 4.9-5.05 (m, 1 H, FC*H*CH_2), 3.9 (dd, 1 H, J = 27, 4 Hz, $H_2NCHCOOH$), 1.6-1.9 (m, 2 H, CH_2CH_3), 1.0 (t, 3 H, J = 7 Hz, CH_3); isomer **51b**: δ 4.9-5.05 (m, 1 H, FC*H*CH_2), 4.1 (dd, 1 H, J = 19, 3 Hz, $H_2NCHCOOH$), 1.5-1.6 (m, 2 H, CH_2CH_3), 1.0 (t, 3 H, J = 7 Hz, CH_3); FAB MS (glycerol), m/z 136.07 (MH^+). Anal. Calcd for $C_5H_{10}NO_2F$: C, 44.44; H, 7.46; N, 10.36. Found: C, 44.32; H, 7.40; N, 10.08. ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ -187.3 to -187.6 (m), and -189.7 to -190 (m).

2-Amino-3-fluorobutanoic Acid (52ab).[30]

Compound **39** (0.10 g, 0.24 mmol) was hydrogenated as described above using 10% Pd/C (0.6 g) to yield 29 mg (> 99%) of **52** as a nearly equal mixture of diastereomers: mp 188-190 °C (dec) (lit.[30] mp 204.5-205 °C (dec)); IR (KBr) 3374-3475 (br), 1648, 1623, 1589 cm^{-1}; ^1H NMR (D_2O, 400 MHz), isomer **52a**: δ 5.0-5.26 (m, 1 H, C*H*F), 4.0 (dd, 1 H, J_{H-F} = 16.5 Hz, J_{H-H} = 3.5 Hz, NC*H*), 1.45-1.55 (dd, 3 H, J_{H-F} = 25 Hz, J_{H-H} = 6.5 Hz, CH_3); isomer **52b**: δ 5.0-5.26 (m, 1 H, C*H*F), 3.74 (dd, 1 H, J_{H-F} = 25.5 Hz, J_{H-H} = 4 Hz, NC*H*), 1.35-1.45 (dd, 3 H, J_{H-F} = 25 Hz, J_{H-H} = 6.5 Hz,

CH_3); FAB MS (glycerol/HCl), m/z 122.12 (MH^+, 100%), 243 (2 MH^+). ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ -181.7 (m), and -184 to -184.5 (m).

2-Amino-3-fluorohexanoic Acid (53ab).[30]

Compound **41** (0.22 g, 0.48 mmol) was hydrogenated as described above using 10% Pd/C (0.15 g) to yield 64 mg (89%) of **53** as a nearly equal mixture of diastereomers: mp 185-190 °C (dec) (lit.[30] mp 180-181 °C (dec)); IR (KBr) 2600-3400 (br), 1655, 1651, 1628, 1609, 1587 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.9-5.2 (m, 1 H, C*H*F), 4.1-3.9 (2 x dd, 1 H, J_{H-F} = 18.5, 27 Hz, J_{H-H} = 3.5, 3.8 Hz, H_2NCH), 1.3-1.9 (m, 4 H, CH_2), 1.0-0.9 (2 x t, 3 H, CH_3); FAB MS (glycerol/HCl), m/z 150 (MH^+, 100%). ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ -210.7 to 210.9 (m) and -213.7 to -214.0 (m).

2-Amino-3-fluoro-5-methylhexanoic Acid (54ab).

Compound **43** (0.18 g, 0.38 mmol) was hydrogenated as described above using 10% Pd/C (0.1 g) to yield 56 mg (91%) of **54** as a nearly equal mixture of diastereomers: mp 164-166 °C. IR (KBr) 3396-3456 (br), 2927, 2962, 1584, 1514, 1407, 1328 cm^{-1}; ^1H NMR (D_2O, 400 MHz) isomer **54a**: δ 5.36-5.58 (m, 1 H, C*H*F), 4.3-4.4 (dd, 1 H, J_{H-F} = 18 Hz, J_{H-H} = 3.4 Hz, H_2NCH); 1.85-2.0 (m, 2 H, CH_2), 1.48-1.85 (m, 1 H, $CH(CH_3)_2$), 1.05 (t, 6 H, J = 6.4 Hz, CH_3); isomer **54b**: δ 5.36-5.58 (m, 1 H, C*H*F) 4.02-4.14 (dd, 1 H, J_{HF} = 27.3 Hz, J_{H-H} = 3.7 Hz, $H_2NCHCOOH$), 1.01 (d, 3 H, J = 2.4 Hz, CH_3), 1.03 (d, 3 H, J = 2 Hz, CH_3); FAB MS (glycerol/HCl), 164.00 (MH^+, 100%). ^{19}F NMR (D_2O, 376 MHz, $CFCl_3$ std) δ -188.0 to -188.3 (m), and -191.8 to -192.1 (m).

(2*S*)-2[(2'-(Benzenesulfonyl)ethyl)amino]-3-hydroxypropanoic Acid (55).

To a solution of L-serine (0.84 g, 8.0 mmol) in 5% aq. $NaHCO_3$ (50 mL) at ~ 50 °C was added phenyl vinyl sulfone (1.41 g, 8.40 mmol). The mixture was stirred 2 h at 50

°C, 1 h at room temperature and acidified to pH ~ 5 with conc. HCl. Lyophilization of the acidic solution gave a solid that was dissolved in water (25 mL). The solution was filtered and lyophilised again. The solid obtained was carefully washed with a minimum amount of water (6 mL) and dried thoroughly *in vacuo* to give 1.31 g (60%) of analytically pure **55**: mp 200-204 °C; $[\alpha]^{24}$ +2.3 (c 1, 1N HCl); IR (KBr cast) 3510, 1626 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 7.7-8.0 (m, 5 H, Ar *H*), 4.0 (m, 2 H, C*H*$_2$OH), 3.85 (t, 2 H, J = 7 Hz, C*H*$_2$SO$_2$), 3.75 (t, 1 H, J = 4 Hz, C*H*NH), 3.5 (t, 2 H, J = 7 Hz, C*H*$_2$N); FAB MS (glycerol/HCl), m/z 274 (MH^+, 100%). Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.35; H, 5.49; N, 5.13; S, 11.72. Found: C, 48.08; H, 5.46; N, 4.91; S, 11.35.

(2*S*)-2[*N*-(2'-(Benzenesulfonyl)ethyl)-*N*-(benzyloxycarbonyl)amino]-3-hydroxypropanoic acid (56).

To a vigorously stirred solution of **55** (1.0 g, 4.0 mmol) in aqueous $NaHCO_3$ ((0.60 g, 7.0 mmol) in water (40 mL)) was added benzyl chloroformate (0.60 mL, 4.2 mmol). After stirring 30 min at room temperature, the mixture was acidified with conc. HCl to pH ~ 2.5 and extracted with EtOAc (4 x 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 0.97 g of syrup, 0.26 g of which were purified by preparative layer chromatography (SiO_2, $CHCl_3$/MeOH/formic acid, 95 /4 /1) to give 0.16 g (20%) of **56**: IR (CH_2Cl_2 cast) 3500, 2940, 1737, 1704, 1305, 1290 cm^{-1}; ^1H NMR (d_6 DMSO, 400 MHz) δ 7.2-7.9 (m, 10 H, Ar *H*), 4.94-5.0 (AB, 2 H, J = 14 Hz, C*H*$_2$Ph), 4.05 (0.5 H, t, J = 7 Hz, C*H*CO), 4.18 (0.5 H, t, J = 7 Hz, C*H*CO), 3.7-3.8 (m, 1 H, C*H*$_2$SO$_2$), 3.6-3.7 (m, 1 H, C*H*$_2$SO$_2$), 3.3-3.6 (m, 4 H, C*H*$_2$N, C*H*$_2$OH), 3.0-3.6 (br s, COO*H*); FAB MS (glycerol/HCl), m/z 408 (MH^+), 430 ($M{\cdot}Na^+$). Satisfactory elemental analysis could not be obtained.

(3*S*)-2[*N*-(2'-(Benzenesulfonyl)ethyl)-*N*-(benzyloxycarbonyl)amino]-3-oxetanone (57).

To a stirred solution of Ph_3P (0.16 g, 0.60 mmol) in THF (2 mL) at -78 °C was added DMAD (0.06 mL, 0.60 mmol). The mixture was stirred 10 min at -78 °C and a solution of **56** (0.23 g, 0.60 mmol) in THF (5 mL) was added over 5 min. The mixture was stirred 1 h at -78 °C and 1 h at 20 °C. The solvent was removed *in vacuo* and the residue was purified by flash chromatography[241] (hexane/45% EtOAc) to give, as a colourless oil, 112 mg (48%) of **57**: IR ($CHCl_3$ cast) 1832, 1707, 1308, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2-7.9 (m, 10 H, Ar *H*), 5.1-5.3 (m, 2 H, C*H*$_2$Ph), 5.0-5.1 (m, 1 H, C*H*CO), 4.6-4.7 (m, 0.5 H, C*H*$_2$O), 4.4-4.5 (m, 1.5 H, C*H*$_2$O), 3.9-4.1 (m, 1 H, C*H*HSO$_2$), 3.3-3.7 (m, 2 H, CH*H*SO$_2$, CH*H*N), 3.15-3.25 (m, 1 H, C*H*HN); FAB MS (glycerol/formic acid), m/z 390 (MH^+). Anal. Calcd for $C_{19}H_{19}NO_6S$: C, 58.61; H, 4.88; N, 3.59; S, 8.22. Found: C, 58.78; H, 4.96; N, 3.57; S, 8.27.

(2*S*)-2-(Benzyloxycarbonyl)amino-3-oxetanone (58).

The literature procedure[67] was used. To a stirred solution of triphenylphosphine (10.5 g, 40.2 mol) in THF (140 mL) and acetonitrile (15 mL) at -55 °C was added dimethyl azodicarboxylate (4.43 mL, 40.2 mmol) over 10 min. The mixture was stirred 10 min at -55 °C and to the resulting slurry was added a solution of Boc-L-serine (8.20 g, 40.0 mmol) in THF (140 mL) and acetonitrile (15 mL). The mixture was stirred at -55 °C for 1 h and at room temperature for 3 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography[241] (32 cm x 5 cm column, hexane/35% EtOAc) to provide 4.5 g, (60%) of **58**: mp 133-134 °C; $[\alpha]^{22}$ -27.5 (c 1, CH_3CN); IR (CH_2Cl_2 cast) 3355, 1847, 1828, 1685, 1530, 1268 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 7.35 (s, 5 H, Ar *H*), 5.5-5.7 (br s, 1 H, N*H*), 5.12 (s, 2 H, C*H*$_2$Ph), 5.0-5.1 (m, 1 H, NC*H*CO), 4.4 (m, 2 H, C*H*$_2$O); exact mass 221.0681 (221.0688 calcd for $C_{11}H_{11}NO_4$). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.71; H, 4.97; N, 6.33. Found C, 59.66; H, 4.92; N, 6.32.

Benzyl [2-(Benzenesulfonyl)ethyl] Ether (59).

A modification of the literature procedure[187] N-alkylation was adapted. To a solution of *N*-(benzyloxycarbonyl)-L-serine (0.12 g, 0.50 mmol) and phenyl vinyl sulfone (84 mg, 0.50 mmol) in THF (7 mL) at 0 °C was added a suspension of NaH (41 mg, 1.7 mmol) in THF (2 mL). THF (5 mL) was added, and the suspension was stirred at 0 °C for 0.5 h and at room temperature for 23 h. The mixture was acidified to pH ~ 1 with 1N HCl, diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give an oil that was purified by reverse phase chromatography (RP-8, 4.5/5.5 CH_3CN/H_2O, v/v as solvent) to give 51 mg (37%) of **59**: IR (MeOH cast) 1300, 1140 cm^{-1}, ^1H NMR (CD_3OD, 300 MHz) δ 7.0-8.0 (m, 10 H, Ar *H*), 4.3 (s, 2H, CH_2Ph), 3.8 (t, 2 H, J = 7 Hz, CH_2SO_2Ph), 3.5 (t, 2 H, J = 7 Hz, OCH_2CH_2); exact mass 276.0818 (276.0820 calcd for $C_{15}H_{16}SO_3$); MS (CI, NH_3), m/z 294 ($M{\cdot}NH_4^+$, 100%).

1-Benzyloxycarbonyl-2-hydroxymethyl-3-oxo-4-benzenesulfonylpyrrolidine (60).

To a stirred solution of lithium hexamethyldisilazide (0.14 mmol, from hexamethyldisilazane (0.03 mL, 0.14 mmol) and BuLi (1.4 M, 0.10 mL, 0.14 mmol) in THF (2 mL) at -78 °C was added a solution of **57** (54 mg, 0.14 mmol) in THF (3 mL) over 5 min. The mixture was stirred 2 h at -78 °C and acetic acid (8 μL, 0.14 mmol) was added. The mixture was warmed to 20 °C, acidified to pH ~ 5 with acetic acid, and extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative layer chromatography (hexane/50% EtOAc) to give 33 mg (61%) of **60**: IR ($CHCl_3$ cast) 3400, 2940, 1764, 1705, 1447, 1419, 1322, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2-7.9 (m, 10 H, Ar *H*), 5.1-5.3 (m, 3 H, CH_2Ph, $CHSO_2Ph$), 4.7 (br t, 1 H, J = 11 Hz, C*H*N), 3.8-4.1 (m,

4 H,C*H*$_2$N, C*H*$_2$OH); FAB MS (Cleland's reagent) m/z 390 (MH^+). A similar reaction in the presence of CuBr·SMe_2 (0.5 equivalents) gave **60** in 20% yield. Satisfactory elemental analysis could not be obtained. Attempted derivatisation as a *tert*-butyl dimethylsilyl ether led to decomposition.

(2*S*,3*R*)-2-(Benzenesulfonyl)amino-3-hydroxybutanoic Acid (61).

This was prepared according to the literature procedure[207] from L-threonine (1.19 g, 10.0 mmol), $PhSO_2Cl$ (1.91 mL, 15.0 mmol) and Na_2CO_3 (3.18 g, 30.0 mmol). The yield was 1.72 g (66%). mp 147-149 °C (lit.[207] mp 146-148 °C); $[\alpha]^{24}$ +10.5 (c 3.2, MeOH); IR (KBr cast) 3444, 3298, 1727, 1449, 1380, 1365 cm^{-1}; ^1H NMR (d_6 acetone, 300 MHz) δ 7.5-7.85 (m, 5 H, Ar *H*), 6.4 (br d, 1 H, J = 9 Hz, N*H*), 4.2-4.3 (dq, 1 H, J = 3, 6 Hz, C*H*CH_3), 3.9 (dd, 1 H, J = 3, 9 Hz, C*H*NH), 1.2 (d, 3 H, J = 6 Hz, C*H*$_3$); FAB MS (glycerol/HCl), m/z 260 (MH^+, 65%).

(2*S*,3*S*)-2-(Benzenesulfonyl)amino-3-hydroxybutanoic Acid (62).

This was prepared according to the literature procedure[207] from L-*allo*-threonine (119 mg, 1.00 mmol), $PhSO_2Cl$ (0.19 mL, 1.50 mmol) and Na_2CO_3 (318 mg, 3.00 mmol). The yield was 180 mg (69%): mp 174-175 °C (lit.[207] mp 176-177 °C); $[\alpha]^{24}$ +17.0 (c 2, MeOH); IR (KBr cast) 3452, 3330, 1728, 1392, 1348 cm^{-1}; ^1H NMR (d_6 acetone, 300 MHz) δ 7.5-7.85 (m, 5 H, Ar *H*), 6.7 (br d, 1 H, J = 9 Hz, NH), 4.0 (m, 1 H,*CH*CH_3), 3.8-3.9 (br dd, 1 H, J = 5, 9 Hz, C*H*NH), 1.2 (d, 3 H, J = 6.3 Hz, C*H*$_3$); FAB MS (glycerol/HCl), m/z 260 (MH^+, 30%).

(4*S*,5*R*)-4-(Benzenesulfonyl)amino-5-methyl-oxazolidin-2-one (63).

To a stirred solution of **61** (65 mg, 0.25 mmol) in THF (9 mL) at 0 °C was added triethylamine (0.090 mL, 0.63 mmol). The mixture was stirred for 5 min and a solution of diphenylphosphoroazidate (0.060 mL, 0.28 mmol) in THF (1 mL) was added. The mixture was then stirred 30 min at 0 °C and then 22 h at room temperature. Water (10 mL) was added, the solution was acidified with formic acid to pH ~ 4, and extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography[241] ($CHCl_3$ 7% MeOH, 0.1% formic acid) to give 27 mg (42%) of **63**: mp 175-177 °C; $[\alpha]^{24}$ -34.0 (c 1, acetone); IR (KBr cast) 3286, 1746, 1718 cm^{-1}; ^1H NMR ($CDCl_3$/d_6 DMSO (50/1, v/v), 360 MHz) δ 8.4-8.5 (d, 1 H, J = 9 Hz, N*H*SO_2Ar), 7.4-8.0 (m, 5 H, Ar *H*), 6.45 (s, 1 H, N*H*CO), 5.0-5.1 (dd, 1 H, J = 6.7 & 6.1 Hz, NHC*H*CH), 4.6-4.7 (m, 1 H, C*H*CH_3), 1.3 (d, 3 H, J = 6.1 Hz, C*H*$_3$); exact mass 256.0525 (256.0518 calcd for $C_{18}H_{12}N_2O_4S$) MS (CI, NH_3), m/z 274 ($M{\cdot}NH_4^+$); FAB MS (glycerol/formic acid), m/z 257 (MH^+). Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93, S, 12.50, Found: C, 46.53; H, 4.58; N, 10.40; S, 12.51.

(*E*) and (*Z*)-1-[*N*-(Benzenesulfonyl)amino]propene (64ab).

To a solution of Ph_3P (525 mg, 2.00 mmol) in THF (10 mL) at -78 °C was added dimethyl azodicarboxylate (0.22 mL, 2.0 mmol). The resulting mixture was stirred at -78 °C for 10 min and a solution of **61** (518 mg, 2.00 mmol) in THF (10 mL) was added over 5 min. The mixture was stirred at -78 °C for 30 min and then at room temperature for 1.5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography[241] (hexane/25% EtOAc) to give 0.18 g (45%) of **64** as a ca. 5:1 mixture of (*E*) and (*Z*) isomers respectively: IR ($CHCl_3$ cast) 3251, 1163, 1145, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (*E*) isomer **64a**: δ 7.5-8.0 (m, 5 H, Ar *H*), 6.2 (br d, 1 H, J = 9 Hz, N*H*), 6.0-6.1 (m, 1 H, NC*H*), 5.0-5.1 (m, 1 H, C*H*CH_3), 1.5-1.6 (dd, 3 H, J = 1.5,

6.5 Hz, C*H*$_3$); (Z) isomer **64b**: δ 7.5-8.0 (m, 5 H, Ar *H*), 6.32 (br d, 1 H, J = 9 Hz, N*H*), 6.0-6.1 (m, 1 H, NC*H*), 4.75-4.85 (m, 1 H, C*H*CH$_3$), 1.45-1.5 (dd, 3 H, J = 1.7, 7 Hz, C*H*$_3$); exact mass 197.0516 (197.0510 calcd for $C_9H_{11}NO_2S$).

Procedure for Preparation of the Tetrabutylammonium salt of (2*S*,3*R*)-2-(Benzenesulfonylamino)-3-hydroxybutanoic Acid (61).

A solution of **61** in anhydrous THF was treated with one equivalent of methanolic tetrabutylammonium hydroxide. The solvent was removed *in vacuo* and the residue was lyophilised. The solid thus obtained was dissolved in anhydrous THF and the solution stored under Ar on molecular sieves.

Trichloroethyl (2*S*,3*R*)-2(Benzenesulfonyl)amino-3-hydroxybutanoate (65).

A solution of *N*-(benzenesulfonyl)-L-threonine tetrabutylammonium salt (prepared from **61** (65 mg, 0.25 mmol) and tetramethylammonium hydroxide (1 M soln in methanol)) in anhydrous THF (10 mL, solution dried overnight on molecular sieves) was cooled to -78 °C and a solution of trichloroethyl chloroformate (0.04 mL, 0.25 mmol) in THF (1 mL) was added. The mixture was stirred at -78 °C for 3 min and triethylamine (0.04 mL, 0.25 mmol) in THF (1 mL) was added. The mixture was then warmed to room temperature and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (SiO_2, benzene/EtOAc/methanol, 7/2/1 v/v) to give 19 mg (19%) of **65**: IR (CH_2Cl_2 cast) 3500, 3300, 1760, 1165, 1138, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.9 (m, 5 H Ar*H*), 5.75 (d, 1 H, J = 8 Hz, N*H*), 4.6 (s, 2 H, C*H*$_2$CCl$_3$), 4.2-4.4 (m, 1 H, C*H*CH$_3$), 4.0 (d, 1 H, J = 6 Hz, NC*H*CO), 1.35 (d, 3 H, J = 6 Hz, C*H*$_3$); MS (CI, NH_3), m/z 407 (M·NH_4^+, M $^{35}Cl_3$), 409 (M·NH_4, M $^{35}Cl_2{}^{37}Cl$).

(4*S*,5*R*)-N-Benzenesulfonyl-4-carboxy-5-methyloxazolidin-2-one (66).

A solution of *N*-(benzenesulfonyl)-L-threonine tetrabutylammonium salt (prepared from **61** (406 mg, 1.60 mmol) and tetramethylammonium hydroxide (1 M soln in methanol)) in anhydrous THF (35 mL, solution dried overnight on molecular sieves) was cooled to -78 °C, and a solution of trichloroethyl chloroformate (0.22 mL, 1.6 mmol) in THF (2 mL) was added. After 3 min, aq NH_3 (28%, 3 mL, 0.050 mol) was added and the mixture was maintained at -78 °C for 5 min, after which it was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, the residue was dissolved in EtOAc, and the solution was stirred briefly with excess ion exchange resin (AG 50 W x 8 (H^+ form)) in water. Drying (Na_2SO_4) and concentration *in vacuo* of the EtOAc solution gave an oil which was purified by flash chromatography[241] ($CHCl_3$/5% MeOH/0.1% formic acid) to give 346 mg (92%) of **66**: mp 165-167 °C; $[\alpha]^{23}$ -31.4 (c 0.5, acetone); IR ($CHCl_3$ cast) 2500-3700 (br), 1783, 1187, 1172 cm^{-1}; ^1H NMR (d_6 acetone, 360 MHz) δ 7.7-8.2 (m, 5 H, Ar *H*), 4.8-4.9 (m, 2 H, C*H*N, C*H*O), 1.55 (d, 3 H, J = 6 Hz, CH_3); ^{13}C NMR ($CDCl_3$/d_6 DMSO (50/1, v/v), 100.6 MHz), δ 168.7 (*C*OOH), 149.9 (*C*ON), 136.4, 133.6, 127.8 (aromatic ring carbons), 73.86 (*C*O), 62.55 (N*C*CO), 19.86 (*C*H_3); MS (CI, NH_3), m/z 303 (M·NH_4^+, 100%), FAB MS (glycerol HCl), m/z 286 (MH^+, 53%) Anal. Calcd for $C_{11}H_{11}NO_6S$: C, 46.31; H, 3.89; N, 4.91; S, 11.24. Found: C, 46.04; H, 3.96; N, 4.84; S, 11.00.

The structure of **66** was confirmed by conversion to the methyl ester **67** with CH_2N_2. To a solution of **66** (10 mg, 0.04 mmol) in acetone (4 mL) was added excess CH_2N_2 in ether. The solvent was removed in vacuo to give 11mg (92%) of **67** as an oil: IR ($CHCl_3$ cast) 1787, 1754, 1368, 1186, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.55-8.2 (m, 5 H, Ar *H*), 4.55-4.61 (m, 2 H, C*H*O, C*H*N), 3.82 (s, 3 H, COOCH_3), 1.55 (d, 3 H, J = 6 Hz, CH_3); MS (CI, NH_3), m/z 317 (M·NH_4^+, 100%).

A similar reacion of the tetrabutylammonium salt of **61** with PhOCOCl/aq NH_3 gave **66** (25%) and **68** (20%).

(2*S*,3*R*)-2-(Benzenesulfonyl)amino-3-hydroxybutanamide (68).

A modification of the literature procedure[207] was used. L-threoninamide hydrochloride (231 mg, 1.50 mmol) and Na_2CO_3 (0.64 g, 6.0 mmol) were dissolved in water (7 mL) and $PhSO_2Cl$ (0.29 mL, 2.3 mmol) was added to the stirred solution. The mixture was stirred vigorously for 5 h at 20 °C. Water (5 mL) was added and the solution was extracted with EtOAc (3 x 5 mL). Drying (Na_2SO_4) and concentration of these extracts provided 84 mg of **68**. The aqueous phase was lyophilised, and the residue was subjected to continuous extraction with EtOAc to furnish an additional 128 mg of product. The total yield was 212 mg (55%): mp 197-198 °C; $[\alpha]^{24}$ +1.5 (c 1, methanol); IR (KBr cast) 1689, 1669, 1329, 1315 cm^{-1}; ^1H NMR (300 MHz, D_2O, NaOD) δ 7.5-7.8 (m, 5 H, Ar *H*), 3.9 (dq, 1 H, J = 4, 6 Hz, C*H*OH), 3.35 (d, 1 H, J = 4 Hz, C*H*NH), 1.05 (d, 3 H, J = 6 Hz, CH_3); FAB MS (glycerol, HCl), m/z 259 (MH^+, 58%). Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.43; N, 10.85, 5, 12.40. Found: C, 46.23; H, 5.40; N, 10.91; S, 12.47.

(3*S*,4*R*)-3-(Benzenesulfonyl)amino-4-methyl-2-oxetanone (69).

A solution of *N*-(benzenesulfonyl)-L-threonine **(61)** (2.07 g, 8.0 mmol) in anhydrous pyridine (28 mL) was cooled to -43 °C and a cold (4 °C) solution of 4-bromobenzenesulfonyl chloride (4.04 g, 15.8 mmol) in anhydrous pyridine (28 mL) was added over 10 min. The mixture was stirred at -43 °C for 45 min, warmed to -10 °C, and poured on crushed ice (ca. 50 g). This was acidified with conc HCl to pH~2. The acidic solution was extracted with EtOAc (3 x 25 mL). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography[241] (hexane /35% EtOAc) to afford 1.05 g (54%) of **69**: mp 113-114 °C; $[\alpha]^{25}$ +24.7 (c 1, CH_2Cl_2); IR ($CHCl_3$ cast) 3280, 1826, 1162, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.9 (m, 5 H , Ar *H*), 5.8 (d, 1 H, J = 9 Hz, N*H*), 5.1 (dd, 1 H, J = 9, 6 Hz, NHC*H*), 4.8-4.9 (m, 1 H, C*H*CH_3), 1.4 (d, 3 H, J = 6 Hz, CH_3); MS (CI, NH_3), m/z 259 ($M{\cdot}NH_4^+$,

100%). Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.79; H, 4.56; N, 5.80; S, 13.28. Found: C, 49.70; H, 4.51; N, 5.71; S, 12.96. (Recrystallization (EtOAc/hexane) of the product obtained after flash chromatography[241] was sometimes necessary. In repeated preparations the yield varied from 40-55%.)

Base hydrolysis of lactone 69

To a stirred solution of **69** (10 mg, 0.04 mmol) in THF (1 mL) was added 1N NaOH (0.09 mL, 0.09 mmol), and the mixture was stirred at 20 °C for 30 min. Acidification to pH ~ 2 with dil. HCl, extraction with EtOAc (3 x 5 mL), drying (Na_2SO_4) and concentration of the combined extracts *in vacuo* gave 10 mg (94%) of a solid that was identical to **61** (^{1}H NMR, IR, MS).

Acid hydrolysis of lactone 69

To a stirred solution of **69** (60 mg, 0.25 mmol) in THF (0.8 mL) at 0 °C was added conc. HCl. The mixture was stirred 30 min at 0 °C, 1h at 20 °C, 1.5h at 50 °C and 2 h at 65 °C. Solvent was removed *in vacuo* and the residue was recrystallized from EtOAc/hexane to give 39 mg (60%) of a solid that was identical to **61** (^{1}H NMR, IR, MS).

(3*S*,4*S*)-3-(Benzenesulfonyl)amino-4-methyl-2-oxetanone (70).

Reaction of N-(benzenesulfonyl)-L-*allo*-threonine **(62)** (259 mg, 1.0 mmol) and 4-bromobenzenesulfonyl chloride (0.512 g, 2.0 mmol) in anhydrous pyridine (7 mL) as described for **61** gave 133 mg (55%) of **70**: mp 114-115 °C; $[\alpha]^{22}$ -19.6 (c 0.5, CH_2Cl_2); IR ($CHCl_3$ cast) 3280, 1832, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.5-8.0 (m, 5 H, Ar *H*), 6.4 (d, 1 H, J = 7 Hz, N*H*), 4.6-4.7 (dq, 1 H, J = 3.8, 7 Hz, C*H*CH_3), 4.4-4.5 (dd, 1 H, J = 3.8, 7 Hz, HNC*H*), 1.58 (d, 3 H, J = 7 Hz, C*H*$_3$); MS (CI, NH_3), m/z 259 (M·NH_4^+). Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.79; H, 4.56; N, 5.80; S, 13.28. Found: C, 49.91; H, 4.74, N, 5.79; S, 13.29.

Base hydrolysis of lactone 70

Compound **70** (10 mg, 0.04 mmol) was hydrolysed with aqueous NaOH as described for **69** to give 10 mg (94%) of a solid that was identical to **62** (^{1}H NMR, IR, MS).

***N*-methyl 2-Aminoethanamide (71).**

The literature procedure[219] was used. To a solution of methylamine (101 g, 3.20 mol) in anhydrous ethanol (360 mL) at 0 °C, was added glycine ethyl ester hydrochloride (30 g, 0.21 mol) in anhydrous ethanol (300 mL). The solution was stirred at 0 °C for 4 h and then at 20 °C for 36 h. It was then concentrated *in vacuo* to 350 mL and ether (900 mL) was added. Cooling at -20 °C for 4 h gave a precipitate that was filtered. The filtrate was concentrated *in vacuo* to give 15.9 g (84%) of **71** as a viscous liquid. IR (film) 3288, 1659, 1546, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.7-7.8 (br s, 1H, NH), 3.32 (s, 2 H, CH_2), 2.8 (d, 3 H, J = 6 Hz $NHCH_3$), 2.1 (s, 2 H, NH_2); MS (CI, NH_3), m/z 89 (MH^+, 64%), 106 ($M{\cdot}NH_4^+$).

***N*-methyl 2-[(Neopentylidene)amino]ethanamide (72).**

The literature procedure[219] was followed. A mixture of **71** (15.9 g, 0.18 mol) and pivaldehyde (24 mL, 0.22 mol) in pentane (300 mL) was heated to reflux for 4.5 h with azeotropic removal of water. The resulting solution was cooled to 20 °C, filtered and the solvent removed *in vacuo* to give 27.4 g (97%) of **72** as a pale yellow oil: IR ($CHCl_3$ cast) 3300, 1663, 1540, 1409 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.6 (t, 1 H, J = 1.5 Hz, CH=N), 7.95 (br s, 1 H, $NHCH_3$), 4.04 (s, 2 H, CH_2), 2.9 (d, 3 H, J = 5 Hz, $NHCH_3$), 2.1 (s, 9 H, $C(CH_3)_3$); exact mass 156.1254 (156.1263 calcd for $C_8H_{16}N_2O$).

(*R*,*S*)-2-(*tert*-Butyl)-3-methylimdazolidin-4-one (73).[219]

To a stirred solution of **72** (27.3 g, 0.17 mol) in anhydrous methanol (90 mL) at 0 °C was added a solution of HCl (65 g, 1.8 mol) in anhydrous methanol (150 mL) over 30 min. The mixture was then stirred overnight at 20 °C. Solvent was removed *in vacuo*, and the resulting solid was suspended in CH_2Cl_2 (300 mL) and washed with 3M NaOH (3 x 100 mL). The combined washings were extracted with CH_2Cl_2 (50 mL) and the organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give 20.7 g (76%) of **73** as a pale yellow oil: IR ($CHCl_3$ cast) 3340, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.14 (d, 1 H, J = 1 Hz, C*H*NH), 3.35-3.54 (m, 2 H, CH_2CO), 2.95 (s, 3 H, NCH_3), 2.25 (br s,1 H, N*H*), 0.95 (s, 9 H, C(CH_3)$_3$); MS (CI, NH_3), m/z 156 (MH^+, 100%).

Resolution of imidazolidinone 73 to 74 and 75

The literature procedure[220] was followed. A suspension of **73** (20.4 g, 0.130 mol) and *S* (+) mandelic acid (20.5 g, 0.130 mol) in acetone (50 mL) was heated till a clear solution was obtained. The solution was then gradually cooled to 20 °C over 6 h and kept at 4 °C for 15 h. The resulting crystals of the (*S*, *S*) diastereomeric salt **74** were filtered and dried *in vacuo*. This salt was used further for the preparation of **76**.

(2*R*)-1-Benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (76).[219]

A suspension of (*S*, *S*) diastereomeric salt **74**, (above) (1.00 g, 3.25 mmol) in CH_2Cl_2 (20 mL) was shaken with NaOH (10 mL, 0.4 M, 4.0 mmol). The CH_2Cl_2 phase was separated, cooled to 0 °C with stirring and treated alternately with NaOH (5 mL, 0.8 M, 4.0 mmol) and benzoyl chloride (0.4 mL, 3.5 mmol) in CH_2Cl_2 (2 mL). After stirring 30 min at 0 °C, the organic phase was separated, washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an oil that solidified upon addtion of ether. This solid was recrystallized twice from ethanol, and the recrystallized material was precipitated from a CH_2Cl_2 solution with pentane to give 0.37 g, (44%) of **76**: mp

142-143 °C; $[\alpha]^{24}$ -126.3 (c 1, CH_2Cl_2) (lit.[219] [α] -126 (c 1, CH_2Cl_2)); IR ($CHCl_3$ cast) 1707, 1652, 1376, 1364 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.4-7.6 (m, 5 H, Ar *H*), 5.6 (s, 1 H, C*H*N), 4.1-4.2 (d, 1 H, J = 15 Hz, CH_2CO), 3.85 (d, 1 H, J = 15 Hz, CH_2CO), 3.05 (s, 3 H, NCH_3), 1.1 (s, 9 H, C(CH_3)$_3$); MS (CI, NH_3), m/z 261 (MH^+, 100%), 278 ($M{\cdot}NH_4^+$, 24%).

(2*R*,5*R*,1'*S*)-1-Benzoyl-2-(*tert*-butyl)-5-(1'-hydroxypropyl)-3-methylimidazolidin-4-one (77).

This was prepared from lithium diisopropylamide (made from diisopropyl amine (0.45 mL, 3.2 mmol) and BuLi (2.0 mL , 1.6 M soln, 3.2 mmol)) in THF (8 mL), (2*R*)-1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (**76**) (0.78 g, 3.0 mmol) in THF (35 mL), and propionaldehyde (0.36 mL , 5.0 mmol) in THF (2 mL) by modification of the literature procedure[114] for condensation of **76** with aldehydes, to give a solid that was purified by flash chromatography[241] (hexane/45% EtOAc) to give **77** as a crystalline solid (798 mg, 84%): IR ($CHCl_3$ cast) 3400, 1682, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.4-7.7 (m, 5 H, Ar *H*), 5.7 (s, 1 H, NC*H*N), 4.46 (d, 1 H, J = 4 Hz, NC*H*CO), 4.14 (d, 1 H, J = 11 Hz, O*H*), 3.08 (s, 3 H, NCH_3), 2.9-3.0 (m, 1 H, C*H*OH), 1.2-1.3 (m, 1H, C*H*HCH$_3$), 1.06 (s, 9H, C(CH_3)$_3$), 0.8-1.0 (m, 1 H, CH*H*CH$_3$), 0.72 (t, 3 H, J = 7 Hz, CH$_3$); MS (CI, NH_3), m/z 319 (MH^+, 100%). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.92; H, 8.17; N, 8.80. Found: C, 67.81; H, 8.18; N, 8.73.

(2*R*,3*S*)-2-Amino-3-hydroxypentanoic Acid (78).

A solution of **77** (0.73 g, 2.3 mmol) in 6 N HCl (25 mL) was heated to reflux for 22 h. The cooled solution was extracted with ether (3 x 20 mL). The aqueous phase was concentrated to give a solid which was purified by ion exchange chromatography (AG 50 x 8, H^+ form, 2% aq NH_3 as eluent) to furnish **78** as a solid, 278 mg (91%): mp 225-227 °C (dec); IR (KBr cast) 3399, 1669, 1637, 1583, 1528 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ

3.96-4.08 (m, 1 H, C*H*OH), 3.7 (d, 1 H, J = 4.5 Hz, NHC*H*), 1.5-1.8 (m, 2 H, CH_2), 1.0 (t, 3 h, J = 7.5 Hz, CH_3); FAB MS (glycerol, HCl), m/z 134 (MH^+). Anal. Calcd for $C_5H_{11}NO_3$: C, 45.11; H, 8.33; N, 10.52. Found: C, 44.75; H, 8.24; N, 10.64.

(2*R*,3*S*)-2-(Benzenesulfonyl)amino-3-hydroxypentanoic Acid (79).

Reaction of **78** (253 mg, 1.9 mmol), Na_2CO_3 (0.6 g, 5.7 mmol) and benzenesulfonyl chloride (0.36 mL , 2.9 mmol) as described for the preparation of **61** gave after recrystallization from EtOAc/petroleum ether, 331 mg (64%) of **79**: mp 138-140 °C; $[\alpha]^{23}$ -17.4 (c 0.5, acetone); IR (KBr cast) 3512, 3328, 1743, 1707, 1328, 1170 cm^{-1}; ^1H NMR (d_6 acetone, 360 MHz) δ 7.5-8.0 (m, 5 H, Ar *H*), 6.35 (d, 1 H, J = 9 Hz, N*H*), 3.9-4.0 (m, 2 H, NC*H*, C*H*OH), 2.4-3.4 (br s, COO*H*), 1.5-1.7 (m, 2 H, CH_2), 0.92 (t, 3 H, J = 7.5 Hz, CH_3); FAB MS (glycerol, HCl) m/z 274 (MH^+, 100%). Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.35; H, 5.53; N, 5.13; S, 11.72. Found: C, 48.57; H, 5.66; N, 5.47; S, 11.78.

(3*R*,4*S*)-3-(Benzenesulfonyl)amino-4-ethyl-2-oxetanone (80).

Reaction of **79** (137 mg, 0.50 mmol) and 4-bromobenzenesulfonyl chloride (256 mg, 1.0 mmol) in anhydrous pyridine (3.5 mL) as described for **69** gave after purification by flash chromatography[241] (hexane/35% EtOAc) 50 mg (39%) of **80**: mp 123-125 °C; $[\alpha]^{23}$ -34.6 (c 0.5, CH_2Cl_2); IR ($CHCl_3$ cast) 3261, 1824, 1345, 1157, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-8.0 (m, 5 H, Ar *H*), 5.48 (d, 1 H, J = 9 Hz, N*H*), 5.1 (dd, 1 H, J = 6, 9 Hz, NHC*H*), 4.55-4.64 (m, 1 H, C*H*O), 1.64-1.82 (m, 2H, CH_2), 1.06 (t, 3 H, J = 7 Hz, CH_3); MS (CI, NH_3), m/z 273 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.76; H, 5.13; N, 5.49; S, 12.55. Found: C, 51.78; H, 5.18; N, 5.47; S, 12.39.

(2*R*,5*R*,1'*S*)-1-Benzoyl-2-(*tert*-butyl)-5-(1'-hydroxy-2'-propenyl)-3-methylimidazolidin-4-one (81).

To a solution of **76** (0.70 g, 2.7 mmol) in THF (30 mL) at -78 °C was added a solution of lithium diisopropyl amide (from diisopropyl amine (0.40 mL, 2.9 mmol) and BuLi (1.8 mL, 1.6 M, 2.9 mmol)) in THF (8 mL). The resulting orange solution was cooled to -95 °C and a solution of acrolein (0.30 mL, 4.6 mmol) in THF (2 mL) was added. The resulting colourless solution was stirred 10 min at -95 °C, half saturated aqueous NH_4Cl (20 mL) was added, and the mixture was stirred 10 min at 20 °C. The aqueous phase was saturated with NaCl and extracted with ether (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give a solid that was purified by flash chromatography[241] (hexane/45% EtOAc) to give 0.70 g (82%) of **81**: mp 152-161 °C; $[\alpha]^{24}$ -122.7 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 3400, 1684, 1636, 1382, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.45-7.75 (m, 5 H, Ar *H*), 5.65 (s, 1 H, NC*H*N), 5.5-5.6 (m, 1 H, C*H*=CH_2), 5.23 (d, 1 H, J = 9 Hz, cis H, CH_2=CH), 5.18 (d, 1 H, J = 14 Hz, trans H, CH_2=CH), 4.74 (d, 1 H, J = 11 Hz, O*H*), 4.52 (d, 1 H, J = 4.5 Hz, NC*H*CO), 3.7-3.8 (m, 1 H, C*H*OH), 3.06 (s, 3 H, NCH_3), 1.05 (s, 9 H, C(CH_3)$_3$); MS (CI, NH_3), m/z 317 (MH^+, 100%). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.11; H, 7.82; N, 8.67.

(2*R*,3*S*)-2-Amino-3-hydroxy-4-pentenoic Acid (82).

The general literature procedure[114] was adapted. A suspension of **81** (166 mg, 0.53 mmol) in 6N HCl (9 mL) was heated to reflux for 16 h. The solution was cooled to 20 °C, diluted with water (5 mL), and extracted with ether (3 x 5 mL). The residue obtained by concentration of the aqueous phase was purified by ion exchange chromatography (AG 50x8, H^+ form, eluted with 2% aqueous NH_3) twice to give 47 mg (67%) of **81**: mp 246-250 °C (dec). IR (KBr cast) 3400, 3600-2300 (br), 1630 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 5.9-6.0 (m, 1 H, C*H*=CH_2), 5.3-5.5 (m, 2 H, CH=CH_2), 4.6-

4.7 (m, 1 H, C*H*OH), 3.7 (d, 1H, J = 4 Hz, C*H*NH_2), FAB MS (glycerol/HCl), m/z 132 (MH^+, 96%).

(2*R*)-1-Benzyloxycarbonyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (83).

The literature procedure[114] was adapted. A solution of **74** (1.5 g, 4.9 mmol) in CH_2Cl_2 (40 mL) was shaken with aqueous NaOH (0.5 M, 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue (662 mg, 4.20 mmol of free amine) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Triethylamine (0.59 mL, 4.2 mmol) and benzyl chloroformate (0.60 mL, 4.2 mmol) were added. After stirring 20 min at 0 °C, the solution was diluted with CH_2Cl_2 (20 mL) and washed with water (3 x 10 mL). The organic phase was dried (Na_2SO_4) and concentrated to give a solid that was recrystallized from CH_2Cl_2 / pentane to give 0.99 g (80%) of **83**: mp 158-159 °C; IR ($CHCl_3$ cast) 1712, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.35 (br s, 5 H, Ar *H*), 5.1-5.2 (AB, 2 H, J = 12 Hz, C*H*$_2$Ph), 5.02 (br s, 1 H, NC*H*N), 4.22 (br d, 1 H, J = 16 Hz, C*H*HCO), 3.82 (br d, 1 H, J = 16 Hz, CH*H*CO), 3.0 (s, 3 H, NC*H*$_3$), 1.03 (br s, 9 H, C(C*H*$_3$)$_3$); MS (CI, NH_3), m/z 291 (MH^+, 100%), 308 ($M{\cdot}NH_4^+$, 55%).

(2*R*,5*R*,1'S)-1-Benzyloxycarbonyl-2-(*tert*-butyl)-5-(1'-hydroxy-2'-propenyl)-3-methylimidazolidin-4-one (84).

This was prepared from **83** (580 mg, 2.00 mmol), lithium diisopropylamide (2.2 mmol, prepared from diisopropyl amine (0.30 mL, 2.2 mmol) and BuLi (1.6 M, 1.4 mL, 2.2 mmol)) and acrolein (0.2 mL, 3.4 mmol) using the procedure described for the preparation of **81**. Purification by flash chromatography[241] (hexane/35% EtOAc) gave 0.47 g (67%) of **84**: mp 82-84 °C; $[\alpha]^{24}$ -51.9 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 3400, 2980, 1708, 1691, 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.3-7.4 (br s, 5 H, Ar *H*), 5.2-5.6 (m, 3 H, C*H*$_2$=C*H*), 5.06-5.2 (m, 2 H, C*H*$_2$Ph), 5.0 (br s, 1H, NC*H*N), 4.86-4.98 (br q, 1 H, C*H*OH), 4.72 (d, 1 H, J = 5 Hz, O*H*), 4.28 (br d, 1 H, J = 19 Hz,

*CH*CO), 3.0 (s, 3 H, NC*H*$_3$), 1.03 (br s, 9 H, C(C*H*$_3$)$_3$); MS (CI, NH_3), m/z 347 (MH^+, 100%). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.71; H, 7.44; N, 7.93.

(2*R*)-1-Benzenesulfonyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (85).

A suspension of **74** (11.0 g, 35.7 mmol) in CH_2Cl_2 (70 mL) was shaken with 1 N NaOH (40 mL). The organic phase was concentrated to a syrup. This was dissolved in THF (50 mL), and the solution was cooled in an ice bath. To the cold solution were added alternately 1N NaOH (45 mL) and $PhSO_2Cl$ (4.60 mL, 35.7 mmol). After stirring 1 h at 20 °C, the solvent was removed *in vacuo* and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from EtOAc/hexane to give 7.8 g (73%) of **85**: mp 184-186 °C; $[\alpha]^{25}$ +16.4 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 1699, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 4.6 (s, 1 H, NC*H*N), 3.8-4.0 (AB, 2 H, J = 17.5 Hz, NC*H*$_2$CO), 2.58 (s, 3 H, NC*H*$_3$), 1.06 (s, 9 H, C(C*H*$_3$)$_3$); MS (CI, NH_3), m/z 297 (MH^+, 98%), 314 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45; S, 10.82. Found: C, 56.88; H, 7.09; N, 9.25; S, 11.21.

(2*R*,3*S*)-2-(Benzenesulfonyl)amino-3-hydroxy-4-pentenoic Acid (86).

This was prepared from **82** (176 mg, 1.30 mmol), $PhSO_2Cl$ (0.25 mL, 1.9 mmol) and Na_2CO_3 (424 mg, 4.00 mmol) in water (5 mL) as described for the preparation of **61**. Purification of the crude product by MPLC (reverse phase, RP-8, H_2O/CH_3CN, 6/4 (v/v), 0.1% formic acid as solvent) gave 50 mg (14%) of **86**: mp 147-149 °C; IR (KBr cast) 3500, 2200-3600 (br), 1732, 1327, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-8.0 (m, 5 H, Ar *H*), 6.4 (d, 1 H, J = 10 Hz, NH), 5.8-5.9 (m, 1 H, *CH*=CH_2), 5.30 (d, 1 H, J = 14 Hz, trans C*H*$_2$), 5.05 (d, 1 H, J = 9 Hz, cis C*H*$_2$), 4.5-4.6 (br m, 1 H, *CH*CO),

4.0 (br m, 1 H, C*H*OH), 2.3-2.7 (br s, COO*H*); FAB MS (glycerol/formic acid), m/z 272 (MH^+, 36%).

(2*S*,3*R*)-2-(Benzenesulfonyl)amino-3-acetoxybutanoic Acid (87) and Its (2*S*,3*S*) Isomer (88).

A solution of **69** (241 mg, 1.00 mmol) and NaOAc (0.41 g, 5.0 mmol) in glacial acetic acid (5 mL) was heated at 55-60 °C for 24 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in 0.1 N HCl (20 mL), and the solution was acidified to pH ~ 3 with 1 N HCl and extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a syrup that was purified by medium pressure liquid chromatography (MPLC) (RP-8, H_2O/CH_3CN 7/3, v/v as solvent) to give **87** and **88** as a 7:1 mixture of diastereomers 155 mg (51%): mp 98-100 °C; IR ($CHCl_3$ cast) 2900-3600 (br), 1742, 1330, 1237, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), major diastereomer **87** (2*S*,3*R*): δ 7.4-8.0 (m, 5 H, Ar *H*), 5.5-6.0 (br, 1 H, COO*H*), 5.42 (d, 1 H, J = 10 Hz, N*H*), 5.3 (dq, 1 H, J = 2.5, 6 Hz, C*H*OAc), 4.0 (dd, 1 H, J = 2.5, 10 Hz, C*H*NH), 2.0 (s, 3 H, $COCH_3$), 1.3 (d, 3 H, J = 6 Hz, CH_3); minor diastereomer **88** (2*S*,3*S*): δ 7.4-8.0 (m, 5 H, Ar *H*), 5.56 (d, 1 H, J = 9 Hz, N*H*), 5.1 (dq, 1 H, J = 4, 6.2 Hz, C*H*OAc), 4.3 (dd, 1 H, J = 4, 9 Hz, C*H*NH), 2.0 (s, 3 H, $COCH_3$), 1.24 (d, 3 H, J = 6.2 Hz, CH_3); MS (CI, NH_3), m/z 319 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{12}H_{15}NO_6S$: C, 47.84; H, 5.02; N, 4.65; S, 10.63. Found: C, 47.63; H, 4.84; N, 4.61; S, 10.45. Hydrolysis (NaOH, H_2O/THF) gave a mixture of **61** and **62** in a 7:1 ratio.

Base hydrolysis of acetates 87 and 88.

To a stirred solution of a 7:1 mixture of **87** and **88** (20. mg, 0.070 mmol) in THF (2 mL) at 20 °C was added 1N NaOH (0.2 mL, 0.2 mmol). The mixture was stirred 30 min at 20 °C, and the solvent was removed *in vacuo*. The residue was dissolved in 0.5 N

HCl (5 mL) and extracted with EtOAc (3 x 1.5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 16 mg (88%) of a solid. Analysis of this solid by ^1H NMR (d_6 Acetone, 360 MHz) indicated it to be a mixture of **61** and **62** in a 7:1 ratio respectively. (This ratio is the same as that for the mixture of **87** and **88**).

(2*S*,3*R*)-(2-(Benzenesulfonyl)amino-3-hydroxy-1-oxobutyl)pyrazole (89).

A solution of **69** (0.12 g, 0.5 mmol) and pyrazole (70. mg, 1.0 mmol) in anhydrous CH_3CN (7 mL) was heated at 60 °C for 4 days. The solvent was removed *in vacuo* and the residue taken up in ether/CH_2Cl_2 (3/1, 30 mL). The resulting suspension was washed with water (3 x 10 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give 116 mg of **89** (75%) as an analytically pure solid: mp 155-157 °C; $[\alpha]^{23}$ +42.8 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 3280, 1735, 1383, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.4-8.0 (m, 8 H, Ar *H*), 6.75-6.85 (d, 1 H, J = 10.5 Hz, N*H*), 5.2 (dd, 1 H, J = 10.5, 3 Hz, NHC*H*), 4.3 (dq, 1 H, J = 6, 3 Hz, C*H*CH_3), 1.34 (d, 3 H, J = 6 Hz, C*H*$_3$); FAB MS (glycerol/formic acid), m/z 309 (MH^+). Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.59; S, 10.35. Found: C, 50.43; H, 4.85; N, 13.29; S, 10.03.

(2*S*,3*R*)-N-Benzyl-2-(benzenesulfonyl)amino-3-hydroxybutanamide (90).

To a solution of benzylamine (0.17 mL , 0.50 mmol) in acetonitrile (5 mL) at -30 °C was added a solution of **69** (0.24 g, 0.50 mmol) in acetonitrile (5 mL). The mixture was slowly warmed to room temperature and then stirred overnight. The solvent was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (25 mL), and this was washed with water (2 x 10 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a solid residue which was recrystallized from EtOAc/hexane to give 0.25 g (72%) of **90**: mp 139-140 °C; $[\alpha]^{23}$ -29.8 (c 0.5, $CHCl_3$); IR ($CHCl_3$ cast) 3000-3600 (br), 1650, 1447, 1320, 1164, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.15-7.9 (m, 10 H,

Ar *H*), 7.0 (br t, 1 H, N*H*CH_2), 5.78 (br d, 1 H, J = 5.5 Hz, N*H*CH), 4.3-4.4 (m, 3 H, C*H*CH_3, C*H*$_2$Ph), 3.6-3.7 (m, 1 H, C*H*NH), 2.65 (br s, 1 H, O*H*), 0.9 (d, 3 H, J = 6.5 Hz, C*H*$_3$); exact mass 348.1143 (348.1143 calcd for $C_{17}H_{20}N_2O_4S$). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.62; H, 5.80; N, 8.08; S, 9.11. A similar reaction of **69** in THF as solvent gave **90** in 80% yield.

Acid Hydrolysis of Amide 90

A suspension of **90** (50 mg, 0.14 mmol) in 6N HCl (10 mL) was heated to reflux for 16 h. The resulting clear solution was cooled to 20 °C, diluted with water (25 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a residue. This was purified by extraction into aqueous $NaHCO_3$ solution and reextraction into EtOAc after acidification of the basic solution to give 19 mg (51%) of **61** that had chromatographic and spectral properties identical to an authentic sample.

Methyl (2*S*,3*R*)-2-(Benzenesulfonylamino)-3-hydroxybutanoate (91).

To a solution of **69** (2.0 mg, 8.3 μmol) in methanol (0.25 mL) at 0 °C was added a solution of NaN_3 (10 mg, 0.15 mmol) in water (0.5 mL). The mixture was warmed to 20 °C, acidified with 1 N H_3PO_4 and extracted with EtOAc (3 x 0.75 mL). Drying (Na_2SO4) and concentration of the combined extracts gave 2.0 mg (91%) of **91** as a solid: mp 99-100 °C; IR ($CHCl_3$ cast) 3500, 3290, 1740, 1330, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.9 (m, 5 H, Ar *H*), 5.5 (br d, 1 H, J = 9.4 Hz, N*H*), 4.1-4.2 (m, 1 H, C*H*OH), 3.8-3.9 (dd, 1 H, J = 9.4, 3 Hz, C*H*NH), 3.48 (s, 3 H, OC*H*$_3$), 2.05 (br d, 1 H, J = 5 Hz, O*H*), 1.27 (d, 3 H, J = 6.3 Hz, C*H*$_3$), FAB MS (glycerol/HCl), m/z 274 (MH^+, 95%).

(2*R*,3*S*)-2-(Benzenesulfonyl)amino-3-isothioureidobutanoic Acid (92).

A solution of **69** (108 mg, 0.45 mmol) in anhydrous acetonitrile (3 mL) was treated with thiourea (38 mg, 0.50 mmol), and the suspension was heated at 60 °C for 72 h. The mixture was then cooled to room temperature and suction filtered to give 100. mg (70%) of **92**: mp 174-175 °C (dec); $[\alpha]^{23}$ +36.4 (c 0.5, 1 N HCl); IR (KBr cast) 3348, 2800-3200 (br), 1659, 1611, 1581, 1390, 1348, 1169 cm^{-1}; ^1H NMR (D_2O, DCl, 360 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 4.4 (d, 1 H, J = 7 Hz, C*H*N), 4.25 (dq, 1 H, J = 7, 6.5 Hz, C*H*CH_3), 1.32 (d, 3 H, J = 6.5 Hz, C*H*$_3$); FAB MS (glycerol/HCl), m/z 318 (MH^+, 100%). Anal. Calcd for $C_{11}H_{15}N_3O_4S_2$: C, 41.62; H, 4.76; N, 13.24; S, 20.20. Found: C, 41.64; H, 4.83; N, 13.12; S, 20.13.

(2*S*,3*R*)-2-(Benzenesulfonyl)amino-3-hydroxybutanethioic acid (93).

To a solution of **69** (0.12 g, 0.50 mmol) in THF (5 mL) at 0 °C was added a suspension of LiSH in THF (0.5 mmol (prepared from BuLi and H_2S)) over 5 min. The resulting pale yellow mixture was stirred at 0 °C for 10 min and then acidified to pH 3 with 1 N H_3PO_4. The aqueous phase was saturated with NaCl and extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to a solid that was recrystallized from EtOAc/hexane to give 115 mg (84%) of **93**: mp 139-141 °C; $[\alpha]^{22}$ -34.6 (c 1, acetone); IR (KBr cast) 3514, 3280, 1692, 1447, 1328, 1165 cm^{-1}; ^1H NMR (d_6 acetone, 360 MHz) δ 7.6-8.0 (m, 5 H, Ar*H*), 6.8 (d, 1 H, J = 8 Hz, N*H*), 4.6-5.3 (br, 1 H, O*H*), 4.3 (dq, 1 H, J = 3, 6 Hz, C*H*CH_3), 4.0 (dd, 1 H, J = 3, 8 Hz, NHC*H*), 2.6-3.2 (br, 1 H, S*H*), 1.02 (d, 3 H, J = 6 Hz, C*H*$_3$); MS (CI, NH_3), m/z 276 (MH^+, 97%); Anal. Calcd for $C_{10}H_{13}NO_4S_2$: C, 43.63; H, 4.76; N, 5.09; S, 23.27. Found: C, 43.63; H, 4.88; N, 4.97; S, 23.03. A similar reaction of **69** with NaSH in H_2O/THF gave **93** in 86% yield.

(4*S*,5*R*)-4-(Benzenesulfonyl)amino-5-hydroxyhexan-3-one (94) and (2*R*,3*S*)-3-(Benzenesulfonyl)amino-4-ethyl-2,4-hexanediol (95).

A solution of **69** (0.24 g, 1.0 mmol) and $CuBr{\cdot}SMe_2$[190] (40. mg, 0.20 mmol) in THF (10 mL) containing dimethyl sulfide (1 mL) was cooled to -23 °C, and a solution of ethylmagnesium chloride in ether (2.8 mL , 4.9 mmol) was added over 5 min. The mixture was maintained at -23 °C for 15 min and poured into cold (4 °C) degassed 0.5 M HCl (30 mL). Methanol (8 mL) was added and the mixture stirred was under Ar for 25 min. The resulting precipitate of CuCl was filtered, and the filtrate was extracted with EtOAc (3 x 25 mL). The combined extracts were washed with saturated EDTA solution (3 x 10 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by MPLC (RP-8, CH_3CN/H_2O, 3/7, v/v) to give **94** (80. mg 30%) and **95** (110 mg 38%). For **94**: mp 132-133 °C; $[\alpha]^{24}$ + 23.8 (c 0.5, $CHCl_3$); IR ($CHCl_3$ cast) 3487, 3283, 1720, 1447, 1325, 1312, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 5.8 (br s, 1 H, N*H*), 4.2-4.3 (m, 1 H, C*H*OH), 3.82 (br s, 1 H, C*H*NH), 2.5-2.6 (m, 1 H, CH_2CH_3), 2.2-2.3 (m, 1 H, CH_2CH_3), 1.24 (d, 3 H, $CHCH_3$), 0.86 (t, 3 H, CH_2CH_3); MS (CI, NH_3), m/z 289 ($M{\cdot}NH_4^+$).

For **95**: IR ($CHCl_3$ cast) 3100-3600, 2972, 2949, 2934, 2884, 1447, 1325, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.4-7.9 (m, 5 H, Ar *H*), 5.3-5.4 (br s, 1 H, N*H*), 4.3 (q, 1 H, J = 6.5 Hz, $CHCH_3$), 3.25 (d, 1 H, J = 8.5 Hz, C*H*NH), 2.4-2.9 (br, 1 H, O*H*), 1.65-1.8 (m, 1 H, CH_2CH_3), 1.5-1.6 (m, 1 H, CH_2CH_3), 1.25-1.5 (m, 2 H, CH_2CH_3), 1.0 (d, 3 H, J = 6 Hz, $CHCH_3$), 0.85 (t, 3 H, J = 7.5 Hz, CH_3), 0.68 (t, 3 H, J = 7.5 Hz, CH_3); MS (CI, NH_3), m/z 319 ($M{\cdot}NH_4^+$, 100%). Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65; S, 10.63. Found: C, 55.84; H, 7.56; N, 4.52; S, 10.44.

(2*S*,3*S*)-2-(Benzensulfonyl)amino-3-bromobutanoic Acid (96).

To a suspension of $MgBr_2 \cdot OEt_2$ (4.0 mmol, prepared from Mg metal (0.10 g, 4.0 mmol) and 1,2-dibromoethane (freshly distilled, 0.36 mL , 4.0 mmol)) in anhydrous ether (16 mL) at room temperature, was added a solution of **69** (241 mg, 1.00 mmol) in anhydrous ether (25 mL) over 5 min. The mixture was stirred at room temperature for 10 min, then cooled in an ice bath and treated with 1N H_3PO_4 (20 mL). The ether phase was separated, and the aqueous phase was extracted with ether (3 x 10 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 0.32 g (> 99%) of pure **96**. Recrystallization could be effected from EtOAc/hexane (88% recovery): mp 140-142 °C; $[\alpha]^{22}$ + 37.6 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 2900-3350, 1724, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 5.55 (d, 1 H, J = 9 Hz, N*H*), 4.0-4.5 (br, 1 H, COO*H*), 4.3 (dq, 1 H, J = 4.4, 7 Hz, C*H*CH_3), 4.2 (dd, 1 H, J = 4.4, 9 Hz, NHC*H*), 1.75 (d, 3 H, J = 8 Hz, C*H*$_3$); FAB MS (glycerol/formic acid), m/z 322, 324 (MH^+ (^{79}Br) (^{81}Br) respectively). Anal. Calcd for $C_{10}H_{12}NO_4SBr$: C, 37.27; H, 3.72; N, 4.35; S, 9.94; Br, 24.84. Found: C, 37.33; H, 3.62; N, 4.31; S, 9.77; Br, 24.80.

(2*S*,3*R*)-2-(Benzenesulfonyl)amino-3-bromobutanoic Acid (97).

This was prepared from $MgBr_2 \cdot OEt_2$ (1.0 mmol) in anhydrous ether (4.0 mL) and **70** (0.06 g, 0.25 mmol) in anhydrous ether (8 mL) as described for the conversion of **69** to **96**. The yield of **97** after recrystallization from EtOAc/hexane was 62 mg (77%): mp 163-165 °C; $[\alpha]^{22}$ -9.1 (c 1, $CHCl_3$); IR (KBr cast) 3320, 1700, 1338, 1171, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 5.4 (d, 1 H, J = 10 Hz, N*H*), 5.3-5.8 (br, 1 H, COO*H*), 4.5 (dq, 1 H, J = 2.5, 7 Hz, C*H*CH_3), 4.2 (dd, 1 H, J = 2.5, 10 Hz, NHC*H*), 1.75 (d, 3 H, J = 7 Hz, C*H*$_3$); FAB MS (glycerol/formic acid), m/z 322, 324 (M^+ (^{79}Br) (^{81}Br) respectively). Anal. Calcd for $C_{10}H_{12}NO_4SBr$: C, 37.27; H, 3.72; N, 4.35; S, 9.94; Br, 24.84. Found: C, 37.12; H, 3.75; N, 4.43; S, 10.24; Br, 24.96.

(2*S*,3*S*)-2-(Benzenesulfonyl)amino-3-chlorobutanoic acid (98).

To a suspension of anhydrous $MgCl_2$ (94 mg, 1.0 mmol) in ether (10 mL) was added a solution of **69** (120 mg, 0.50 mmol) in anhydrous ether (11 mL). Tetrabutylammonium chloride (132 mg, 0.50 mmol) was added, and the mixture was stirred at room temperature for 2 weeks after which the solvent was removed *in vacuo*. The residue was taken up in 1N H_3PO_4 (10 mL), and the solution was extracted with EtOAc (3 x 15 mL). The combined EtOAc extracts were stirred with an aqueous slurry of excess ion exchange resin (AG 50 x 8 (H^+ form)), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was recrystallized from EtOAc/hexane to give 108 mg (78%) of **98**: mp 129-131 °C; $[\alpha]^{23}$ +35.7 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 3340, 3200-3400 (br), 1725, 1334, 1166, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 6.8-7.2 (br, 1 H, COO*H*), 5.62 (d, 1 H, J = 9.3 Hz, N*H*), 4.2-4.3 (m, 2 H, C*H*CH_3, NC*H*CO), 1.6 (d, 3 H, J = 6.5 Hz, C*H*$_3$); FAB MS (glycerol/formic acid), m/z 278 (MH^+). Anal. Calcd for $C_{10}H_{12}NO_4SCl$: C, 43.40; H, 4.34; N, 5.06; S, 11.57; Cl, 12.84. Found: C, 43.22; H, 4.27; N, 4.79; S, 11.53; Cl, 12.67.

(2*S*,3*S*)-2-(Benzenesulfonyl)amino-3-iodobutanoic Acid (99).

This was prepared from $MgI_2 \cdot OEt_2$ (0.55 mmol, prepared from Mg metal (24 mg, ~ 1.0 mmol) and 1, 2 diiodoethane (155 mg, 0.55 mmol)) in anhydrous ether (7 mL , protected from light) and **69** (0.12 g, 0.50 mmol) in anhydrous ether (10 mL) as described for **96** to give a yellow oil that solidified at -20 °C. This was dissolved in a minimum amount of EtOAc and excess hexane (ca 15 vol) was added to give after cooling a pale buff coloured solid, 154 mg (83%): mp 149-150 °C; $[\alpha]^{22}$ +50.8 (c 1, $CHCl_3$); IR ($CHCl_3$ cast) 2800-3500 (br), 1722, 1162, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-8.0 (m, 5 H, Ar *H*), 6.4 (d, 1 H, J = 8.5 Hz, N*H*), 4.4 (dq, 1 H, J = 4.2, 6.5 Hz, C*H*CH_3), 3.9 (dd, 1 H, J = 4.2, 8.5 Hz, C*H*NH), 1.95 (d, 3 H, J = 6.5 Hz, C*H*$_3$); FAB MS

(glycerol/HCl), m/z 370 (MH^+). The compound was light sensitive and a satisfactory analysis could not be obtained.

(2*R*,3*R*)-2-(Benzenesulfonyl)amino-3-bromopentanoic Acid (100).

This was prepared from $MgBr_2 \cdot OEt_2$ (0.65 mmol) in anhydrous ether (3.0 mL) and **80** (41 mg, 0.16 mmol) in anhydrous ether (7 mL) as described for the conversion of **69** to **96**. The yield of **100** was 44 mg (80%) after recrystallization: mp 142-143 °C; $[\alpha]^{23}$ -36.8 (c 0.5, $CHCl_3$); IR ($CHCl_3$ cast) 3290, 1707, 1450, 1342, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.9 (m, 5 H, Ar *H*), 5.54 (d, 1 H, J = 9 Hz, N*H*), 4.3 (dd, 1 H, J = 4, 9 Hz, C*H*NH), 4.0-4.1 (m, 1 H, C*H*Br), 3.4-4.0 (br, COO*H*), 1.9-2.1 (m, 2 H, CH_2CH_3), 1.08 (t, 3 H, J = 7.5 Hz, CH_3); FAB MS (glycerol/HCl), m/z 336, 338 (MH^+, (^{79}Br) (^{81}Br) respectively). Anal. Calcd for $C_{11}H_{14}NO_4SBr$: C, 39.28; H, 4.20; N, 4.17; S, 9.54; Br, 23.53. Found: C, 38.85; H, 4.25; N, 4.01; S, 9.76; Br, 23.38.

2-Amino-3-bromobutyric Acid Hydrobromide (101).

The general literature procedure[227] was adapted. A suspension of **96** (0.20 g, 0.62 mmol) and phenol (106 mg, 1.10 mmol) in 48% aq HBr (7 mL) was heated to reflux for 10 min. The solution was cooled to 20 °C, diluted with water (10 mL), and extracted with ether (2 x 10 mL) and $CHCl_3$ (10 mL). The aqueous phase was concentrated *in vacuo* to give 127 mg (78%) of **101**: mp 181-182 °C; $[\alpha]^{24}$ -6.2 (c 1, H_2O); IR (KBr cast) 3440, 2970, 1735, 1481, 1201 cm^{-1}; ^1H NMR (D_2O, 360 MHz) 1:1 mixture of diastereomers, δ 4.65-4.75 (m, 1 H, C*H*CH_3), 4.36 (d, 1 H, J = 3 Hz, C*H*NH) 4.3 (d, 1 H, J = 3.5 Hz, C*H*NH), 1.84 (d, 3 H, J = 7 Hz, CH_3), 1.86 (d, 3 H, J = 7 Hz, CH_3); FAB MS (glycerol/HCl), m/z 182 (MH^+ ^{79}Br, 100%), 184 (MH^+, ^{81}Br, 98%) for free amino acid.

(*E*)-2-(N-(Benzenesulfonyl)amino)-2-butenoic Acid (102) and Its (*Z*) Isomer (103).

To a solution of $Bu_2Cu(CN)Li_2$ (prepared from CuCN (143 mg, 1.60 mmol) and BuLi (3.2 mmol) over 40 min at -23 °C) in THF (5 mL) at -78 °C was added a solution of **96** (240 mg, 0.75 mmol) in THF (6 mL). The mixture was warmed to 0 °C for 3 h and then to room temperature overnight. The mixture was quenched and extracted as described for the preparation of **94** to give an oil that was purified by MPLC (RP-8, CH_3CN/H_2O, 3/7, v/v, 0.1%, CF_3COOH). Concentration of the fractions *in vacuo* gave 80. mg of the (*E*)-isomer **102** (44%) and 15 mg of the (*Z*)-isomer **103**. A similar reaction of **96** at -21 °C for 22 h gave only the (*E*)-isomer **102** and unreacted **96** (15%). Less than 1% (*Z*)-isomer could be dected under the latter conditions. For (*E*)-isomer **102**: mp 104-106 °C; IR ($CHCl_3$ cast) 2800-3600 (br), 1697, 1443, 1409, 1155, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.8 (m, 5 H, Ar *H*), 6.75 (q, 1 H, J = 8 Hz, CH_3CH), 6.5 (br s, 1 H, N*H*), 2.1 (d, 3 H, J = 8 Hz, CH_3); FAB MS (glycerol/HCl), m/z 242 (MH^+); Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.79; H, 4.56; N, 5.80; S, 13.28. Found: C, 49.84; H, 4.31; N, 5.67; S, 13.00.

For (Z)-isomer **103**: IR ($CHCl_3$ cast) 2800-3600 (br), 1686, 1403, 1332, 1279, 1169, 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.5-7.8 (m, 5 H, Ar *H*), 7.1 (q, 1 H, CH_3CH), 6.0 (br s, 1 H, N*H*), 2.08 (d, 3 H, CH_3); FAB MS (glycerol, HCl), m/z 242 (MH^+).

Methyl 2,5-Bis(benzylideneamino)pentanoate (104).

The procedure of Bey et al[231] was adapted. To a suspension of methyl ornithinate dihydrochloride (6.5 g, 30 mmol) in dichloromethane (20 mL) was added benzaldehyde (6.1 mL, 60 mmol) and triethylamine (8.4 mL, 60 mmol). The mixture was stirred 15 h at room temperature and was then concentrated *in vacuo*. The residue was suspended in anhydrous ether (200 mL) and filtered. The filterate was washed with water (5 x 20 mL)

and brine, and was dried (Na_2SO_4). Concentration *in vacuo* gave 8.6 g (89%) of **104** as a pale yellow oil: IR ($CHCl_3$ cast) 1738, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 8.25 (br s, 2 H, PhC*H*), 7.5-8.0 (m, 4 H, Ar *H*), 7.25-7.5 (m, 4 H, Ar *H*), 4.05 (t, 1 H, J = 6 Hz, C*H*CH_2), 3.7 (s, 3 H, COOC*H*$_3$), 3.62 (t, 2 H, J = 6 Hz, C*H*$_2$N), 1.5-2.25 (m, 4 H, C*H*$_2$); exact mass 263.1546 (263.1548 calcd for $C_{18}H_{19}N_2$ (M-$COOCH_3$)).

Methyl 2,5-Bis(benzylideneamino)-2-methylpentanoate (105).

The literature procedure[231] was adapted. To a solution of lithium diisopropylamide (from diisopropylamine (1.4 mL, 10 mmol) and BuLi (6.40 mL, 1.56 M, 10.0 mmol)) in THF (80 mL) at -78 °C was added a solution of **104** (3.2 g, 10 mmol) in THF (15 mL). The mixture was stirred 15 min at -78 °C, methyl iodide (2.0 mL, 32 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 4.5 h. Water (50 mL) was added. The aqueous phase was saturated with NaCl and extracted with ether (2 x 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 3.3 g of an oil that was characterized as crude **105**: IR ($CHCl_3$ cast) 1730, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 8.27 (s, 2 H, C*H*Ph), 7.5-8.0 (m, 4 H, Ar *H*), 7.25-7.5 (m, 4 H, Ar *H*), 3.75 (s, 3 H, COOC*H*$_3$), 3.67(t, 2 H, C*H*$_2$N), 1.5-2.5 (m, 4 H, C*H*$_2$), 1.55 (s, 3 H, C*H*$_3$); exact mass 277.1699 (277.1705 calcd for $C_{19}H_{21}N_2$ (M-CO_2CH_3)).

2,5-Diamino-2-methylpentanoic Acid (107).[231]

Compound **105** (3.3 g, ~ 10 mmol) was dissolved in ether/THF (5/1, v/v, 60 mL) and stirred with 2 M HCl (50 mL) for 27 h at room temperature. The aqueous phase was separated, washed with ether (50 mL), and concentrated *in vacuo* to give a solid that was characterized as methyl 2,5-diamino-2-methylpentanoate dihydrochloride **(106)** by ^1H NMR. ^1H NMR (D_2O, 80 MHz) δ 3.9 (s, 3 H, COOC*H*$_3$), 3.07 (t, 2 H, J = 6 Hz, C*H*$_2$$NH_2$), 1.5-2.25 (m, 4 H, C*H*$_2$), 1.65 (s, 3 H, C*H*$_3$).

The above solid was dissolved in 6 M HCl (100 mL) and the solution heated to reflux for 16 h. The solution was then concentrated *in vacuo*, and the residue was purified by ion exchange chromatography (AG 50 x 8, H^+ form, 1 M aqueous NH_3 as eluent) to give 1.2 g (82%) of **107**: mp 138-140 °C; IR (KBr cast) 2300-3800 (br), 1630 cm^{-1}; ^1H NMR (D_2O, NaOD, 400 MHz) δ 2.6 (t, 2 H, J = 7 Hz, C*H*$_2$N), 1.6-1.7 (m, 1 H, C*H*HCH$_2$N), 1.35-1.5 (m, 2 H, CH*H*CH$_2$N, C*H*HCH$_2$), 1.2-1.35 (m, 1 H, CH*H*CH$_2$), 1.22 (s, 3 H, C*H*$_3$); FAB MS (glycerol/formic acid), m/z 147 (MH^+, 100%).

Methyl 2,5-Bis(acetylamino)-2-methylpentanoate (108).

A modification of the literature procedure procedure[233] was used for acetylation. The α-methylornithine (**107**) (35 mg, 0.24 mmol) was dissolved in 1N NaOH (1 mL, 1 mmol), and acetic anhydride (1.0 mL, 10.5 mmol) and 1N NaOH (2 mL, 2 mmol) were added in alternate portions. The mixture was stirred at 20 °C for 2.5 h, acidified with conc. HCl to pH ~ 1.5, and concentrated *in vacuo* to give a crystalline residue. This was extracted with boiling acetone (50 mL). Concentration of the extract gave a solid which was dissolved in methanol and treated with excess diazomethane in ether. The methanol was removd *in vacuo* and the residue was partiotined between dichloromethane and water. Concentration of the aqueous phase provided 0.040 g (70%) of **108**: IR (CH_2Cl_2 cast) 1740, 1650, 1547 cm^{-1}; ^1H NMR (D_2O, 80 MHz) δ 3.63 (s, 3 H, COOC*H*$_3$), 3.22 (br t, 2 H, C*H*$_2$N), 2.0 (s, 6 H, COC*H*$_3$), 1.2-1.9 (m, 4 H, C*H*$_2$), 1.45 (s, 3 H, α C*H*$_3$); exact mass 244.1424 (244.1424 calcd for $C_{11}H_{20}N_2O_4$).

Methyl 2,6-Bis(acetylamino)-2-methylhexanoate (109).

The procedure used for the preparation of **108** was adapted. The α-methyl lysine (0.04 g, 0.25 mmol) was dissolved in 1 mL 2N NaOH, and acetic anhydride (0.53 g, 5.1 mmole) and 2N NaOH (3 mL, 6 mmol) were added in alternate portions. The mixture was stirred at 20 °C for 2 h, acidified with conc. HCl to pH ~ 1.5, and concentrated *in vacuo* to

give a crystalline residue. This was extracted with 50 mL boiling acetone. Concentration of the extract gave a solid which was dissolved in methanol and treated with excess diazomethane in ether. The methanol was removed *in vacuo* and the residue was partitioned between $CHCl_3$ and water. Concentration of the aqueous phase provided 57 mg (88%) of **109** as a hygroscopic solid: IR ($CHCl_3$ cast) 1740, 1650, 1548 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 3.76 (s, 3 H, $COOCH_3$), 3.18 (t, 2 H, CH_2N), 1.95 (s, 6 H, $COCH_3$) 1.2-1.9 (m, 6 H, CH_2), 1.44 (s, 3 H, α CH_3); exact mass 258.1579 (258.1579 calcd for $C_{12}H_{22}N_2O_4$).

Methyl 2,5-bis(acetylamino)pentanoate (110).

This was prepared from methyl ornithinate dihydrochloride by adaptation of the procedure used to prepare **111**, to give 0.590 g (56%) of **110** after purification by chromatography (SiO_2, $CHCl_3$): mp 113.5-115 °C; IR ($CHCl_3$ cast) 1749, 1653, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 6.5-6.7 (br d, 1 H, α N*H*), 6.1-6.3 (br s, 1 H, δ N*H*), 4.4-4.8 (m, 1 H, α *H*), 3.76 (s, 3 H, $COOCH_3$), 3.38 (q, 2 H, δ CH_2), 2.06 (s, 3 H, $COCH_3$), 2.0 (s, 3 H, $COCH_3$), 1.4-1.9 (m, 4 H, CH_2); exact mass 230.1264 (230.1267 calcd for $C_{10}H_{18}N_2O_4$).

Methyl 2,6-Bis(acetylamino)hexanoate (111).[237]

This was prepared by modification of the literature procedure.[236] Triethylamine (2.1 mL, 15 mmol) was added to a stirred suspension of methyl lysinate dihydrochloride (1.00 g, 4.28 mmol) in $CHCl_3$ (25 mL). Acetic anhydride (1.4 mL, 15 mmol) was added, and stirring was continued at 20 °C for 24 h. The mixture was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and the aqueous phase was reextracted with $CHCl_3$ (20 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography[241] (SiO_2, $CHCl_3$, 8% MeOH) to give 0.36 g (34%) of **111**: mp 95-96 °C; IR (CH_2Cl_2 cast) 1734, 1651, 1547 cm^{-1}; ^1H NMR

($CDCl_3$, 360 MHz) δ 6.25 (br d, 1 H, α N*H*), 5.75 (br s, 1 H, ε N*H*), 4.6-4.8 (m, 1 H, α *H*), 3.76 (s, 3 H, COOCH_3), 3.1-3.3 (m, 2 H, CH_2), 2.05 (s, 3 H, COCH_3), 1.98 (s, 3 H, COCH_3), 1.2-1.9 (m, 6 H, CH_2). Exact mass 244.1423 (244.1423 calcd for $C_{11}H_{20}N_2O_4$). Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.08; H., 8.25; N, 11.47. Found: C, 54.20; H, 8.38; N, 11.30.

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Appendix

The α-methyl ornithine was tested by Dr. M. A. Pickard (Department of Microbiology, University of Alberta) as a transport inhibitor of ornithine, lysine and arginine in *Escherichia coli* and *Bacillus sphaericus*. It was observed[230] that only ornithine transport was selectively inhibited, but only at high molar excesses (10- and 100-fold larger) than that of ornithine. Analogous inhibition of lysine transport by α-methyl lysine was observed. The inability of α-methyl analogues to cause significant inhibition of amino acid transport suggests that the active site of the transport complex in these bacteria is stringent in its steric demands.

In order to check for possible contamination of α-methyl ornithine and α-methyl lysine by ornithine and lysine, respectively, these compounds were analysed as the N, N'-diacetyl methyl esters. Gas chromatography-mass spectrometric (GC-MS) analysis of the α-methyl derivatives showed no detectable signal due to the corresponding N, N'-diacetyl methyl ester derivatives of ornithine and lysine.

For capillary gas chromatography all compounds were injected as solutions in methanol. The results are presented in Table 7 and show that the maximum possible contamination of the α-methyl amino acid by the parent compound (α-H) is 0.2%.

Table 7. Gas chromatographic analysis of derivatives of ornithine, lysine and their α-methyl analogues.

Compound	Retention time (min)	Run parameters
Methyl N, N'-diacetylornithinate	22.34	Injection temp. 140 °C heating rate 2 °C/min, final temp. 200 °C. Carrier gas (N_2), 9.3 psi.
Methyl N, N'-diacetyl-α-methyl ornithinate	20.04	
Methyl N, N'-diacetyllysinate	10.58	Injection temp. 180 °C heating rate 2 °C/min, final temp. 220 °C. Carrier gas (N_2), 9.6 psi.
Methyl N, N'-diacetyl-α-methyl lysinate	8.97	