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THE UNIVERSITY OF ALBERTA

Solid Supports For Azodicarboxylates In Mitsunobu Reactions And Synthesis of α-Amino Acids.

by 

Hanaa Ibrahim Assil

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

Department of Chemistry

EDMONTON, ALBERTA

Spring 1989

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Supervisor

Date: Jan 4, 1989

To my Parents

and

Mahmoud

ABSTRACT

The use of polymer-supported alkyl azodicarboxylates in Mitsunobu reactions was investigated. Initial studies employed aminopropyl silica gel which reacted with 2,4-dinitro-1,5-difluorobenzene to attach a monofluorobenzene moiety. This, however, failed to undergo nucleophilic substitution by aminopropanol, and further functionalization was not possible. A hydroxymethyl polystyrene was prepared from the commercially available chloromethyl polystyrene (Biobeads S-X1, 3.9 mequiv/g, 50.1 mol% loading) by reaction with potassium acetate in dimethyl acetamide (80 °C, 20 h) followed by treatment with anhydrous hydrazine (25 °C, 20h). Activation of the resulting hydroxyl group with phosgene in presence of pyridine followed by treatment with methyl carbazate in dichloromethane containing 4-(dimethylamino)pyridine produced the methyl hydrazodicarboxylate polystyrene. Oxidation to the azo form was possible using chlorine gas, chlorine water, dinitrogen tetroxide, and N-bromosuccinimide with pyridine (1 h, 25 °C). The latter reagent was found to be most rapid and effective. The resulting methyl azodicarboxylate polystyrene **17** could be reduced and reoxidized for at least 5 cycles without degradation, and had no tendency to explode or ignite when subjected to severe mechanical shock or high temperatures. The number of accessible azodicarboxylate units was determined by reaction with excess Ph_3P followed by water and ^1H NMR analysis of the resulting Ph_3P/Ph_3PO ratio.

The alkyl azodicarboxylate polystyrene reagent **17** was efficient in performing a variety of Mitsunobu reactions. N-(*tert*-Butoxycarbonyl)-L-serine was converted to its β-lactone (50% yield) using triphenylphosphine and **17** (1.2 equiv, THF, 25 °C). This β-lactone is easily attacked by n-propylamine (THF, 0 °C, 98% yield) and ammonia (THF, 0 °C, 81%). However, attempts to prepare a diaminopimelic acid analog through ring opening of the β-lactone by N-(*tert*-butoxycarbonyl)-2,3-diaminopropionic acid (KH, THF, 0 °C) gave only 3% yield of the desired product. The polymer-supported reagent **17**

(1.0-1.2 equiv) was also employed in esterification (THF, 25 °C, 20 h) of benzoic acid by benzyl alcohol and n-propanol to yield the corresponding esters in 61 and 55% yields, respectively. Ethyl cyanoacetate reacted with n-propanol (THF, 20 °C) in presence of **17** (1.0 equiv) to give ethyl 2-cyanopentanoate in 42% yield. Reaction of phthalimide with benzyl alcohol using **17** (1.0 equiv, 25 °C, THF) afforded N-benzylphthalimide in 57% yield. N-Phthaloyl-D-alanine ethyl ester was prepared from (S)-(-)-ethyl lactate in presence of **17** (1.3 equiv, THF, 20 °C, 48 h) in 45% yield. The polymer-supported azodicarboxylate **17** (1.1 equiv, THF, 20 °C) was also efficient in dehydrosulfurization of N, N'-diphenylthiourea to the corresponding carbodiimide. Zearalenone dimethyl ether was hydrolyzed and re-lactonized in presence of **17** (1.7 equiv, THF, 25 °C) to give its enantiomer in 42% yield. This polystyrene-supported reagent is, therefore, a potentially useful replacement for the soluble dialkyl azodicarboxylates in industrial-scale reactions.

ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. John C. Vederas, for his guidance and continuous encouragement and support through the course of this work. I am grateful to Sunil V. Pansare and all the co-workers in the research group for helpful discussions. My gratitude especially goes to Dr. Bernard Rawlings and Dr. Lister Lam for their assistance in obtaining 2D-NMR data. The staff of the spectral and analytical services in the Chemistry Department of the University of Alberta are thanked for their assistance in characterizing compounds. Finally, I would like to thank my husband, Mahmoud, for his endless support and encouragement through all stages of this work.

Financial support from the University of Alberta is gratefully acknowledged.

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LIST OF ABBREVIATIONS

Cbz	Benzyloxycarbonyl
bp	Boiling point
Boc	Butoxycarbonyl
C.E.	Crown ether
CI	Chemical ionization
DEAD	Diethyl azodicarboxylate
DFDNB	1,5-Difluoro-2,4-dinitrobenzene
DMAD	Dimethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
EI	Electron impact
IR	Infrared
LDA	Lithium diisopropylamide
Me	Methyl
MPLC	Medium pressure liquid chromatography
MS	Mass spectra
mp	Melting point
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
POSFAB	Positive fast atom bombardment
Pyr	Pyridine
TSP	Sodium trimethylsilylpropionate

THF	Tetrahydrofuran
TMS	Tetramethylsilane
TLC	Thin layer chromatography
Et_3N	Triethylamine

INTRODUCTION

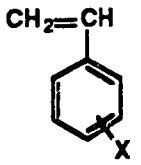
A great deal of interest is currently focused on organic reactions performed in the presence of chemically reactive species attached to insoluble solid supports. Several reviews have been published on the use of solid supports in chemical reactions,[1-7] in phase transfer catalysis,[4, 8-10] and in asymmetric synthesis.[11] Solid supports are utilized in synthesis of polypeptides,[12, 13] oligonucleotides,[14, 15] and oligosaccharides.[16] Various applications are also found in biochemistry[17] (enzyme immobilization and affinity chromatography), analytical chemistry (pH indicators, electrode modifiers), and pharmaceutical and agricultural chemistry.[16] The interest of this laboratory in diaminopimelic acid analogs[18] and Mitsunobu reactions[19-21] led to an examination of the application of solid supports and polymer chemistry to these two areas.

A reagent or substrate attached to an insoluble support has several practical advantages.[7] One of the most important is that product isolation is simplified because the supported species are easily separated from the non-supported ones by filtration. Separation is easiest if the polymer is cross-linked (and therefore insoluble in all media) and in the form of beads at least 50μ in diameter.[3] This makes it possible, in some cases, to avoid chromatographic separation or exposure of the reaction product(s) to water. If the use of an excess of the reagent results in a greater yield, unconsumed polymer-bound starting material is easily recovered. Similarly, recovery of the spent reagent makes recycling possible which can be economically very worthwhile, especially with complex or relatively inaccessible materials. Such processes are often readily amenable to automation. In addition, crosslinked polymers are generally non-volatile and, therefore, non-toxic and odourless. Hence, reactions involving thiols or selenium compounds on polymer supports are environmentally more acceptable.[7]

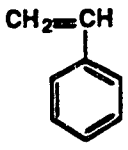
Solid supports are utilized in enzymology for immobilizing enzymes. This has the advantage that the protein, which is often expensive or difficult to obtain, can be easily recovered and reused. In addition, polymer-bound enzymes often have enhanced storage stability. This subject has been extensively reviewed.[7, 17] Another application in enzymology is affinity chromatography, which is based on reversible binding of the enzyme to a substrate analog (inhibitor) that is permanently attached to a solid support. Since enzymes normally operate in aqueous solutions, they are usually bound to hydrophilic supports. The support is generally a derivative of a natural polysaccharide (as in agarose and sephadex) or a derivative of a synthetic polyacrylamide.[17]

Ideally, the support should be physically and chemically stable under the reaction conditions and completely insoluble in all solvents used. Polystyrenes crosslinked with divinylbenzene (1-2 %) are the most widely used carriers owing to their facile functionalization and their chemical and mechanical stabilities.[6] Inorganic oxides, in particular silica, silica-alumina mixtures,[7] and controlled pore glass[13,15] are also excellent support materials. Polysaccharides (agarose, sephadex) and polyacrylamide beads find extensive applications as solid supports in affinity chromatography.[17]

Functionalized cross-linked polymers are generally prepared either by copolymerization of monomers containing the required functional groups or chemical modification of preformed polymers.[3] Copolymerization involves an appropriate functionalized monomer, a monomer used as diluent, and a cross-linking agent.[3] For example, copolymerization of polystyrene resins utilizes a functional styrene monomer A and a diluent B.[7] In general, such polymerizations employ radical initiators such as 2,2'-



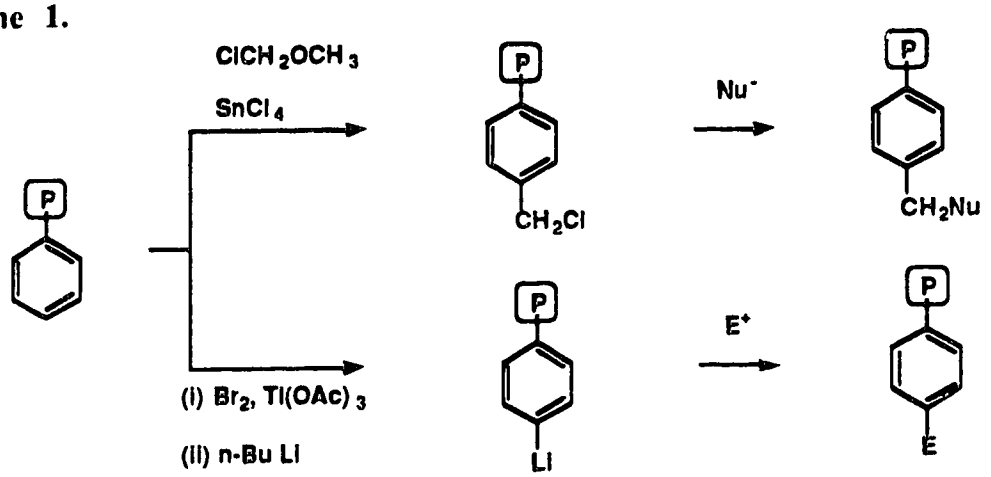
A



B

azobisisobutyronitrile or benzoyl peroxide.[7] Polymers can also be prepared by chemical modification of commercially available cross-linked polystyrenes.[3, 4, 7, 22] The two most versatile routes for chemical modification of polystyrene proceed via chloromethylation or lithiation (Scheme 1).[1, 7, 22]

Scheme 1.



Chloromethyl polystyrene resin is prepared by electrophilic aromatic substitution using chloromethyl methyl ether in presence of stannic chloride as a catalyst. Attack by various nucleophiles affords functionalized polystyrene supported reagents.[23] Several functional groups are also immobilized by lithiation of polystyrenes and subsequent attack by electrophiles. For example, the polymer-supported phosphine (Fig. 1), which is used in combination with azodicarboxylates for Mitsunobu reactions,[24] is prepared by chemical modification of lithiated polystyrenes.[25]

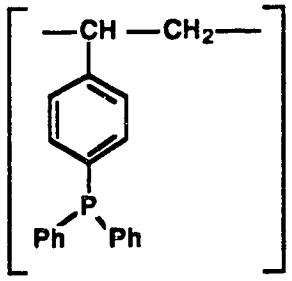
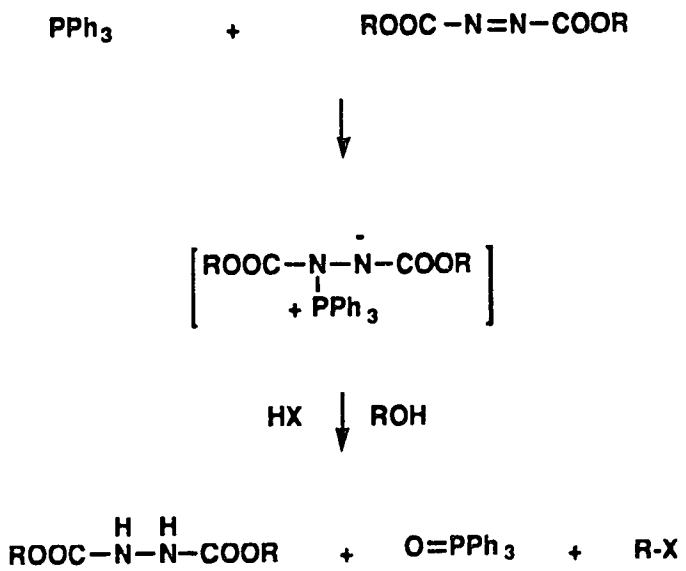


Fig.1 Polystyryldiphenylphosphine

Elemental microanalysis and infrared absorption spectroscopy (IR) are the two most powerful analytical techniques for characterization of functionalized supports.[7] Routine combustion analysis can be applied to organic supports such as functionalized polystyrenes. In the case of inorganic oxides, this technique is also useful, although there is always an inorganic residue. Infrared spectroscopy is an excellent qualitative probe for following the progress of reactions with organic polymers. Unfortunately, in the case of macromolecular inorganic oxides, much of the useful absorption range for organic functional group detection is masked by broad absorption bands in the region below ~1500 cm^{-1}. Other methods of characterization like titration,[7] iodometry,[26] and ^{13}C nuclear magnetic resonance (NMR)[1] are also used where appropriate.

Polymer-supported reagents could, in principle, be very helpful in a widely used reaction like the Mitsunobu reaction.[27] This involves the activation of an alcohol by the adduct of triphenylphosphine and a dialkyl azodicarboxylate (Scheme 2). Attack by

Scheme 2.



carbon, nitrogen, or oxygen nucleophiles leads to displacement of the hydroxyl group. This process proceeds under mild conditions with high stereospecificity and functional

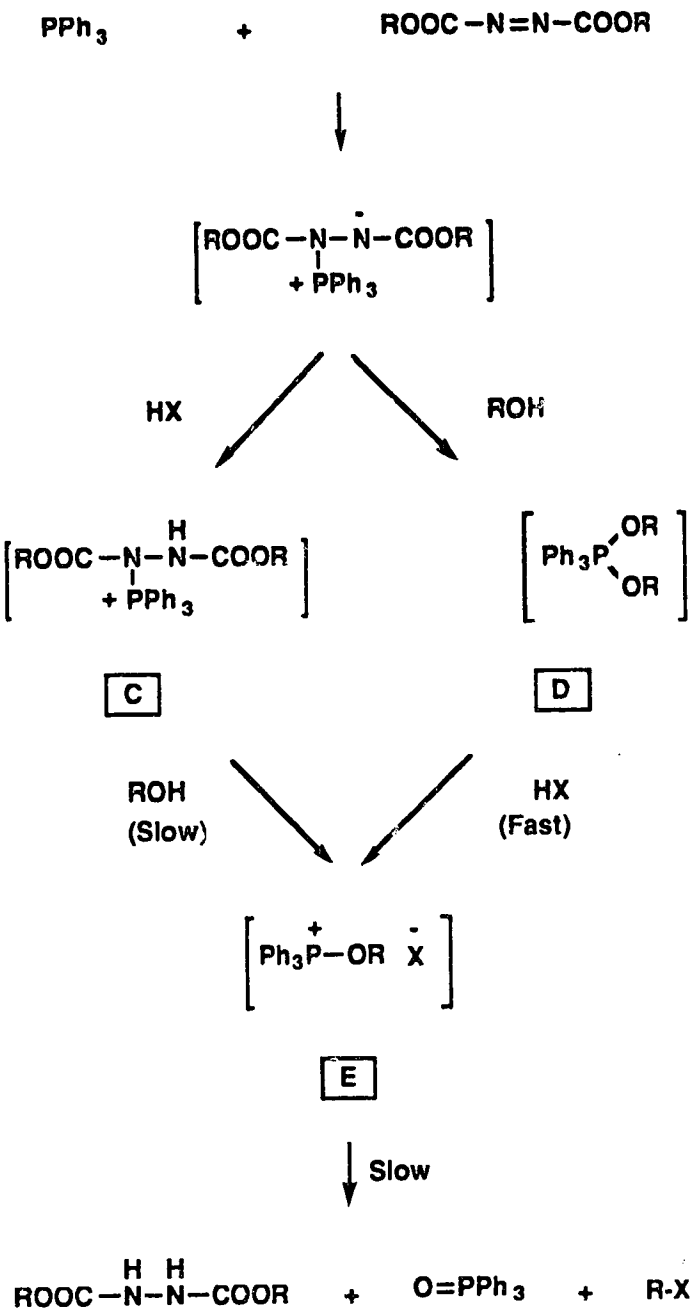
selectivity. It has been applied in synthesis of macrolide antibiotics,[28] nucleosides (including azidothymidine (AZT)) and nucleotides,[29] amino acids,[30] amino sugars, steroids, natural products, and various heterocycles[31] including monobactam antibiotics and precursors of other important lactams.[32]

The major limitations of industrial scale application of the Mitsunobu reaction are associated with the azodicarboxylate reagent.[32a] These include the expense of the azodicarboxylates, the tendency of some of them to explode during distillation,[33] and difficulties in separation of any unconsumed reagent and its reduced form from the desired products. Polymer-supported phenylphosphines[24] assist the separation of products, but immobilization of the more expensive alkyl azodicarboxylate appears much more desirable because the recovered polymer could possibly be recycled several times without difficulty.

The mechanism of the Mitsunobu reaction has been extensively studied[34, 35] and is believed to occur as outlined in Scheme 3. The first step is formation of the adduct between the azodicarboxylate and triphenylphosphine, a process which occurs within seconds at - 20 °C. ^{31}P NMR data established that the phosphorus is bonded to nitrogen and not to oxygen.[34a]

The second step in the Mitsunobu esterification is alcohol activation.[34a] The ^{31}P NMR studies by Grochowski et al.[34b] and von Itzstein and Jenkins[34c] indicate that the dialkoxy phosphorane **D** is formed as an intermediate and decomposes in presence of acid to form the products. The intermediate between the dialkoxy phosphorane and the products is considered to be the alkoxy phosphonium salt **E**.[34c] However, additional ^{31}P NMR studies by Varasi et al.[35a] show that the presence or absence of the acid component during mixing of the other reactants is a key variable in the mechanism of the reaction and that the dialkoxy phosphorane **D** is only an intermediate in the special case when the acid is added last.

Scheme 3.

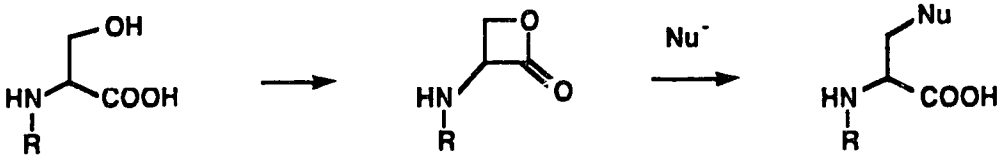


The final step in Mitsunobu esterification is the nucleophilic substitution reaction of the X^- anion with the oxyphosphonium intermediate E. The counterion generated in forming C acts as a base to deprotonate the alcohol. This must occur before attack on the phosphorous of the triphenylphosphonium group can take place. The reaction is known to

proceed with stereochemical inversion (S_N2). However, elimination is a competitive process. When it occurs, E2 is the suggested mechanism and only one isomer (Z) is formed.[34a] Varasi et al.[35a] also found that addition of sodium benzoate to **E** in presence of X^- does not form the expected benzoate ester, but rather leads to rapid formation of RX even when X^- is the trifluoroacetate anion. The alkoxy phosphonium salt **E** is, therefore, inaccessible to external nucleophiles and is thought to exist as a tight ion pair. Addition of sodium benzoate probably disrupts these stable aggregates allowing attack of the closely held X^- on a neighbouring alkoxy group.[35a] The dramatic increase in the rate of formation of RX on addition of sodium benzoate was explained by general base catalysis of the process of formation of **E** from **C**.

The Mitsunobu conditions were used in our laboratories to cyclize β-hydroxy acids **1** to β-lactones **2** in good yields (60-72%) (Scheme 4).[19] This process was shown to proceed by inversion of configuration.[20] The importance of these β-lactones is due to the

Scheme 4.

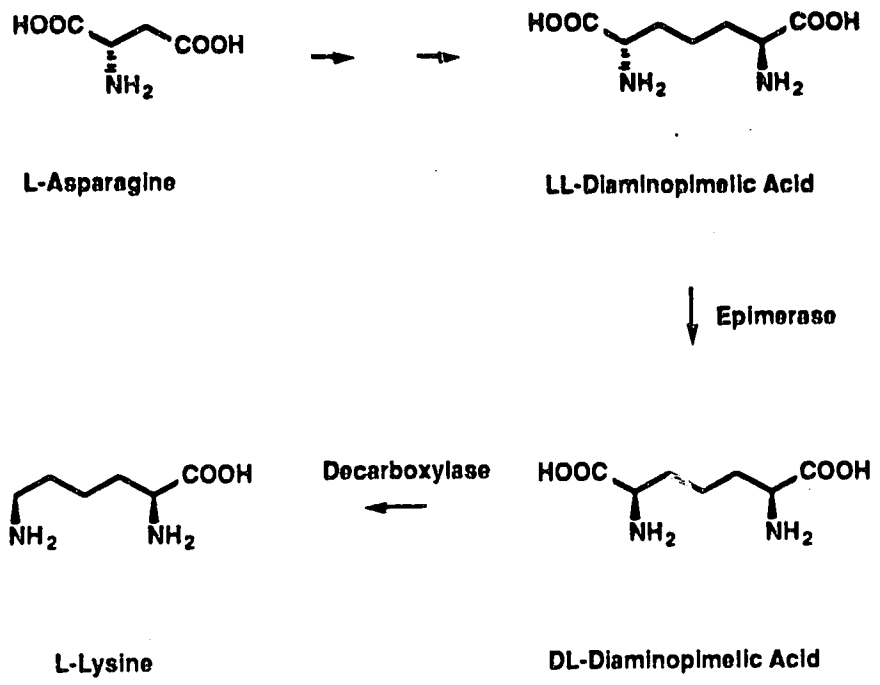


1 **2**

fact that nucleophilic ring opening provides a route to the synthesis of chiral β-substituted alanines.[19] Thus, a polymer-bound azodicarboxylate could be utilized in the synthesis of β-lactones which, in turn, act as synthetic precursors to various α-amino acids.

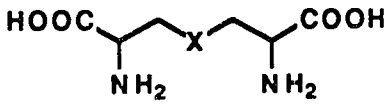
An α-amino acid of interest to us[18] is 2,6 diaminopimelic acid (Scheme 5).[36-40] It is the immediate biosynthetic precursor of L-lysine in bacteria[37a] and green plants.[37b] Although L-lysine is universally required for protein biosynthesis and is involved in cross-linking the cell walls of many gram-positive bacteria, it is an essential dietary amino acid for mammals. Therefore, diaminopimelic acid analogs which disrupt diaminopimelate

Scheme 5.



metabolism should be selectively lethal to bacteria through inhibition of both lysine production and cell wall biosynthesis.[38a, 39] Indeed, several diaminopimelic acid analogs have been synthesized and found to be antibacterial agents.[18, 40]

Lanthionine, a sulfur analog of diaminopimelic acid, is a competitive inhibitor of the diaminopimelate epimerase[18a] and decarboxylase[18b] enzymes. Replacement of sulfur

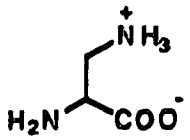


X = CH_2 2,6-Diaminopimelic acid

X = S Lanthionine

by nitrogen could, potentially, afford inhibitors of diaminopimelate enzymes with interesting antibiotic activity. In addition, presence of nitrogen at this position in the molecule makes it possible to attach the compound to an affinity column for use in

purification of the enzymes. Attachment in the center of the molecule is necessary since any change at either end of diaminopimelate prevents the enzymes from recognizing the substrate. A possible synthesis of such nitrogen analogs would involve attack of N-protected serine β-lactones (available from the Mitsunobu reaction, Scheme 4), by a derivative of 2,3-diaminopropionic acid.



2,3-diaminopropionic acid.

The Mitsunobu reaction is applied in several synthetic approaches which could render a polymer-bound azodicarboxylate especially useful. Alkylation of active methylene carbons[41] is a route to carbon-carbon bond formation, while alkylation of nitrogen nucleophiles[42] could lead to synthesis of N-protected α-amino acids. Dehydrosulfurization of thioamides under Mitsunobu conditions affords nitriles[43] or ketenimines,[44] while thioureas provide carbodiimides.[45,46] Esterification reactions,[27] which proceed with inversion of configuration, are applied to cyclization of hydroxy acids for preparation of stereoisomers of macrolide antibiotics not easily obtained in nature.[28]

The main aim of this project is the preparation of a polymer-bound alkyl azodicarboxylate and demonstration of its applicability in Mitsunobu reactions, including the preparation of β-lactones, which provide a route to nitrogen analogs of diaminopimelic acid. An analytical method of characterization and accurate determination of available active sites is, of course, essential.

RESULTS AND DISCUSSION

A. SYNTHESIS OF POLYMER-SUPPORTED ALKYL AZODICARBOXYLATES.

An ideal polymeric support matrix should be insoluble in most solvents for easy separation, mechanically stable to physical manipulations, and inert to reaction conditions. The reactions used for the chemical modifications must be essentially free of side reactions, since there is no way of removing the undesirable products which become bound to the polymer.[5] The materials generally used as solid supports in organic synthesis are either inorganic supports (silica, glass) or derivatives of cross-linked polystyrenes. Although these compounds are similar in their porous nature, there are significant differences in other properties: effect of solvent, loading capabilities, mechanical stability, and stability towards temperature and pH changes.[7, 47]

The choice of reaction solvent is of particular importance, especially in the case of polystyrenes. In a polymer-supported reagent, the vast majority of functional groups are within the polymer beads.[3] The choice of solvent defines the degree of swelling of the beads. This, in turn, affects the degree of diffusion of the substrates into the polymer which then determines the chemical reactivity of the immobilized molecules.[6] The extent of swelling with a given solvent depends on the support polymer, the functional groups present and on the concentration and distribution of both.[3] Thus, the choice of solvent can have an important influence on the physical nature of the molecules bound to the polystyrene matrix.[6] In contrast to low cross-linked polystyrene and derivatives of polyacrylamide, silica and glass beads are rigid and not subject to swelling and, thus, the accessibility of functional groups is not determined by the choice of solvent.[6, 15a]

However, in this case, hydrogen bonding may have considerable influence on the physical properties of the immobilized molecules.[6]

A significant difference between organic and inorganic solid supports is in their loading capabilities. Lightly cross-linked polystyrenes are the best. They contain approximately 10 mmol/g of aromatic groups which, on complete functionalization, can lead to a high functional group loading. The low loading capabilities of inorganic oxides like silica are among the disadvantages that prevent their widespread use. This is due to the fact that the surface hydroxyl groups, through which functionalization is accomplished, are typically 5 per 100 $Å^2$ of surface.[5, 7] Thus inorganic matrices have an upper limit of monofunctional groups of 1-2 mequiv/g of polymer.[6]

Mechanical stability depends on the kind of material and the nature of the mechanical stress.[15a] Inorganic supports have a rigid network and can generally withstand mechanical pressure and sudden changes in solvent polarity.[7] In contrast, polystyrenes are affected by high flow rates of solvents and have to be stirred at low velocities to avoid mechanical degradation.

Temperature stability is another factor to be considered in the choice of suitable materials for a solid support. Organic polymers undergo degradation at temperatures approximately 150 °C while inorganic materials are quite stable at much higher temperatures. Polystyrene supports are inert over a large range of pH which often makes them more useful, since many inorganic oxides actually dissolve in highly alkaline or acidic solutions.[7]

Polystyrenes are readily available, hydrophobic (therefore compatible with many organic solvents), and contain unfunctionalized phenyl residues that are inert to most chemical reactions.[3] However, they have several disadvantages.[7] In derivatizing cross-linked polymers, it is often difficult to control the degree of loading of the polystyrene. Some reagents do not diffuse into the cross-linked network easily, and chemical transformations become unreliable and difficult to reproduce. The structural changes which

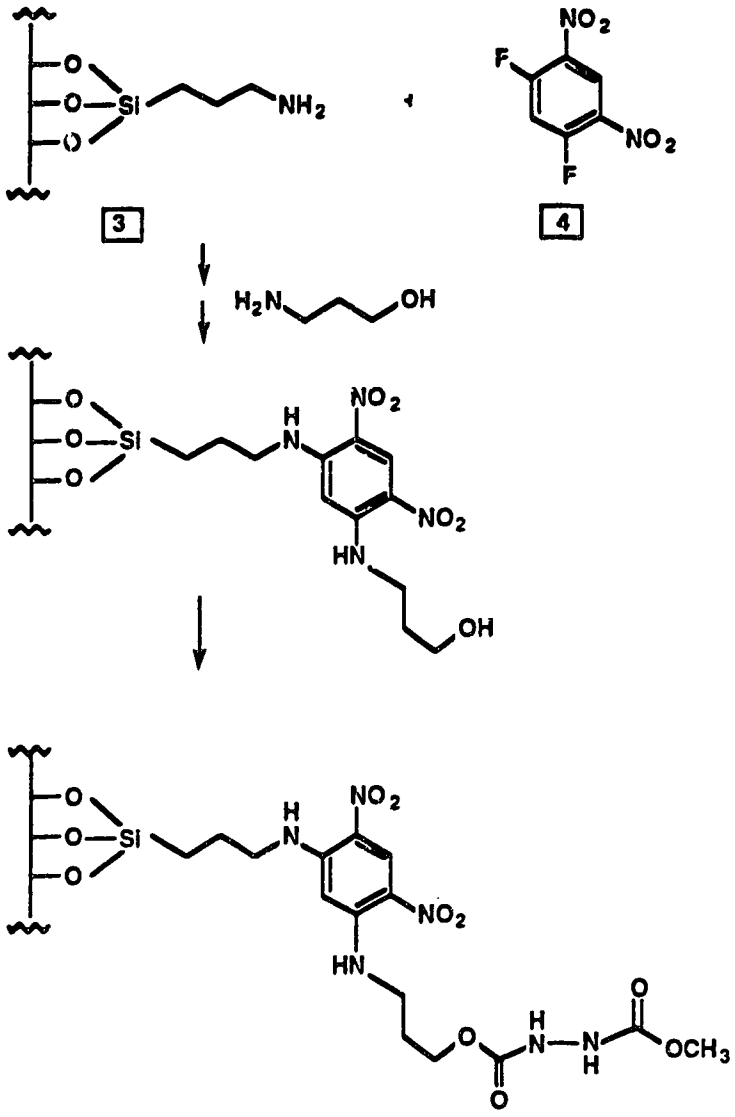
take place during the chemical modification can also be difficult to characterize. In contrast to polystyrene resins, silica gel is not subject to swelling. It has high mechanical strength and thermal stability and is insoluble in most solvents. In addition, silica gel is also a low-cost starting material and is readily available.[48] In this work, the use of both silica gel and cross-linked polystyrenes as supports for azodicarboxylates is considered.

Functionalization of Silica Gel and Preparation of Model Compounds.

Various forms of amorphous silica exist.[7] They are all products of the polycondensation of orthosilicic acid, $Si(OH)_4$, with the general formula $SiO_2.xH_2O$. The surface of silica gel contains silanol -OH groups and -O- strained siloxane atoms.[49] The main disadvantage of using modified silica in organic synthesis is that Si-O-C bond is highly polarized and, thus, very sensitive to reagents containing free hydroxyl groups, especially water. This difficulty can be overcome by attaching a carbon chain to the silica surface to form Si-O-Si-C bonds, which are more stable against an attack by electrophilic or nucleophilic agents than the Si-O-C bonds.[6] Thus, to functionalize silica gel, it is initially refluxed with 35% hydrochloric acid to transform the -O- strained siloxane atoms into -OH. Silica gel, activated in this manner, reacts with alkyl trialkoxy silanes to afford alkyl functionalized silica gel[6, 7, 49] which can be further modified.

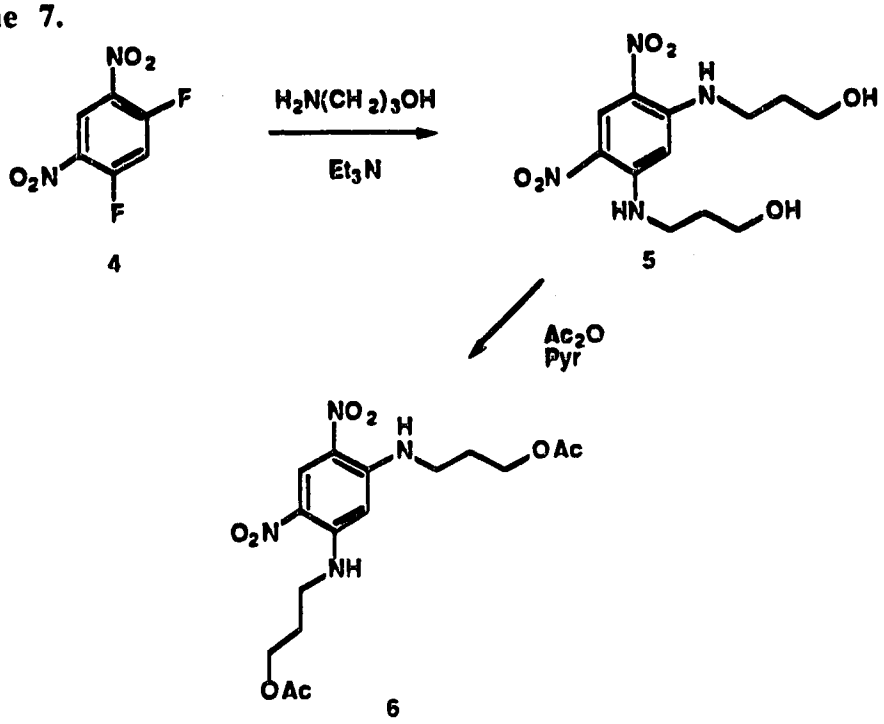
Initial studies centered on functionalization of commercially available 3-aminopropyl silica gel **3** (Sigma) to generate a supported alkyl hydrazodicarboxylate which could, in principle, be oxidized to the azodicarboxylate (Scheme 6). The commercially available 1,5 difluoro-2,4-dinitrobenzene (DFDNB) (**4**) is a useful cross-linking agent[50] and appeared to be a possible linking arm for the hydrazo moiety.

Scheme 6.



To test this, the synthesis of a model compound for the silica gel-supported reagent was attempted using the sequence shown in Scheme 7. Reaction of 1,5-difluoro-2,4-dinitrobenzene (**4**) with 3-aminopropanol (2 equiv) affords the diol **5** in 70% yield. Attempts to protect the nitrogens using acetic anhydride resulted in exclusive O-acetylation to give **6** in quantitative yield. The NMR signal for the -NH protons was still present even when reaction time was extended from 4 h to 24 h. However, the acetyl group is not ideal for protection because of possible N to O acyl transfer and the necessity of additional steps

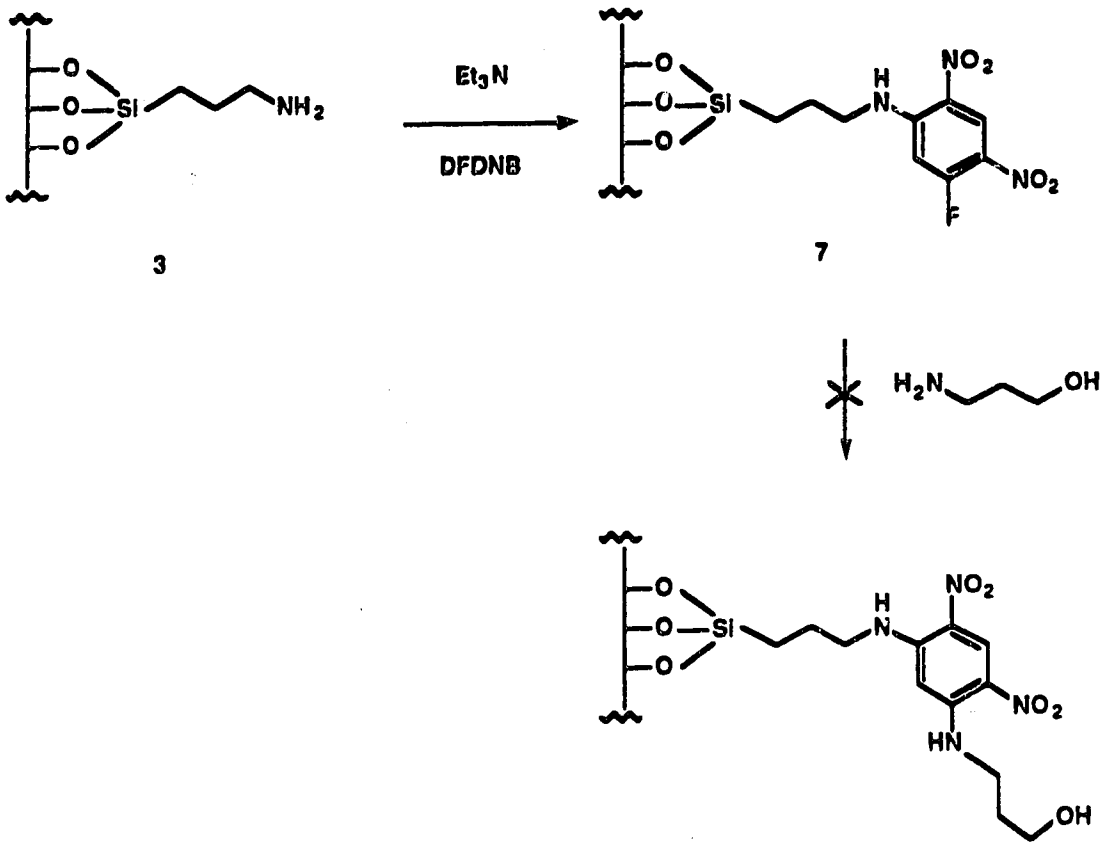
Scheme 7.



to generate the reagent. Hence, a direct functionalization sequence without protection was employed on silica gel.

The aminopropyl silica gel **3** reacts with 1,5-difluoro-2,4-dinitrobenzene (**4**) to give **7** (Scheme 8). Elemental analysis of **7** indicates that only one fluorine was replaced. However, attempts to functionalize the silica gel further, using 3-aminopropanol, did not succeed, as indicated by elemental analysis. Since similar substitution reactions on **4** are successful,[50] the difficulties probably arise not from lack of reactivity of the monofluorobenzene moiety in **7**, but rather from steric hindrance which prevents attack by the amino group. A longer linking arm between the silica polymer and the substituted benzene may be the necessary factor to overcome this problem. Alternatively, the evolution of F^- during the initial reaction may be having a drastic effect on the silica gel network, although this does not appear to be an obstacle in the first step. In any case, difficulties

Scheme 8.



3 7

with elemental analysis of the products and the relatively small number of reactive sites per unit weight encouraged the exploration of polystyrene-functionalized reagents.

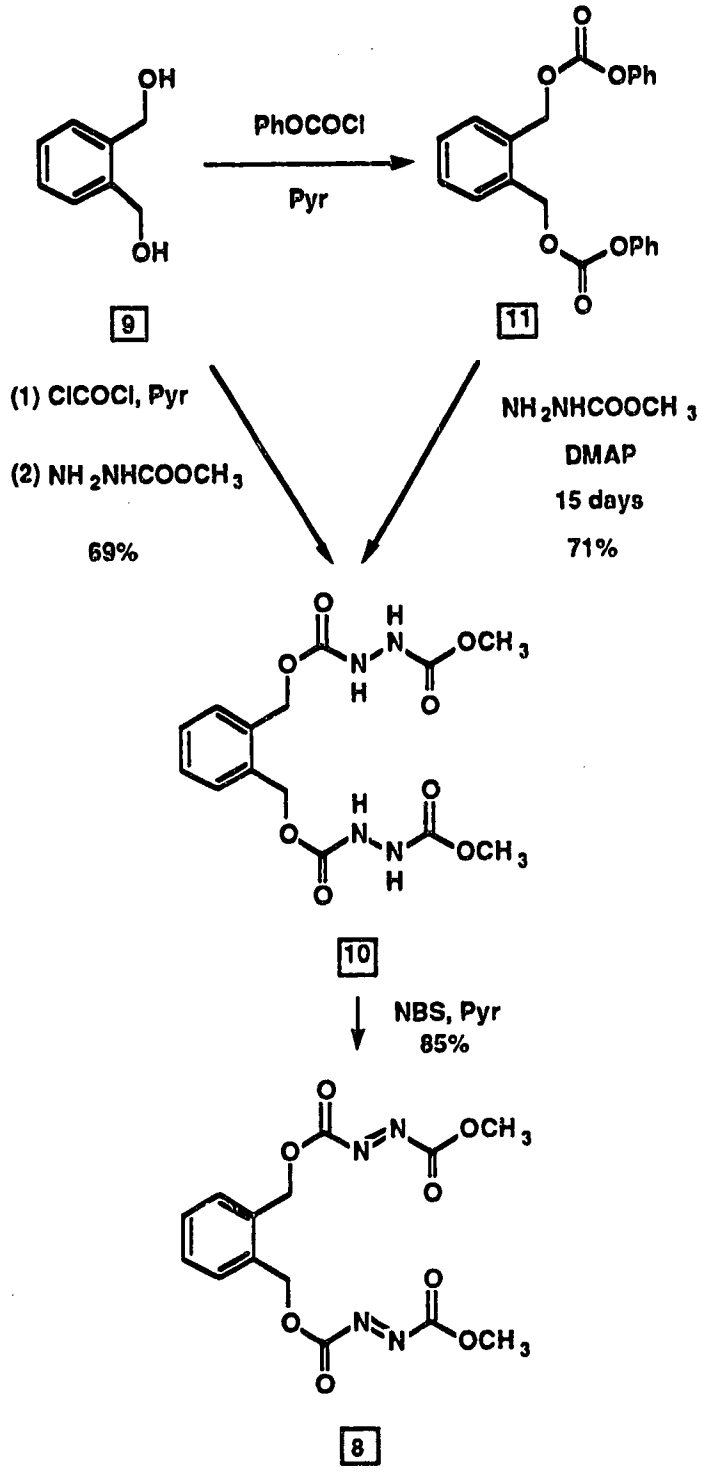
Functionalization of Polystyrene and Preparation of Model Compounds.

Polystyrenes are particularly attractive as supports and have a wide range of applications.[4,7,16] They appear to be ideal for immobilization of alkyl azodicarboxylates since they are known to be easy to functionalize and their polymeric backbone should be inert to Mitsunobu reaction conditions.

Polystyrenes containing hydroxymethyl groups are commercially available. Thus, a model compound **8** was chosen as target to mimic the reactions which could effect the

conversion of hydroxymethyl groups to the alkyl azodicarboxylate on the functionalized polystyrene (Scheme 9). Such a low molecular weight soluble compound is easy to detect

Scheme 9.



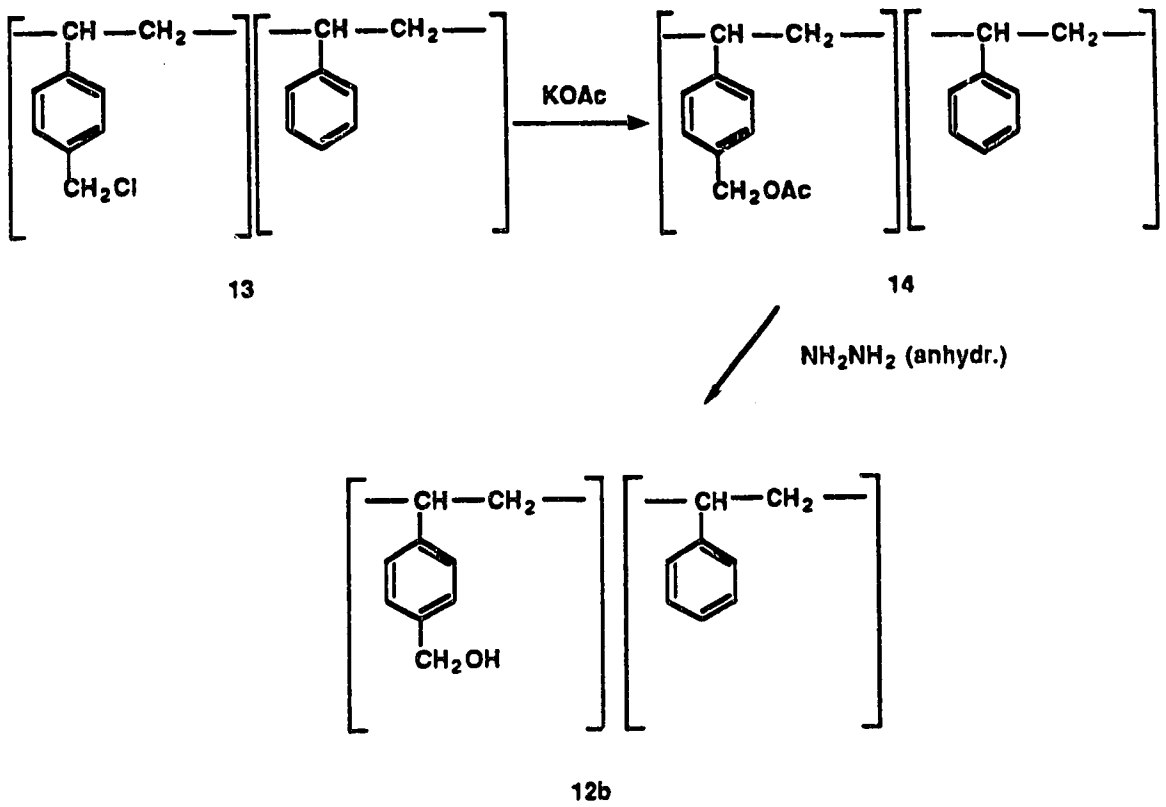
using ordinary thin layer chromatographic techniques and can be easily characterized using standard NMR spectra. Therefore, it is possible to follow closely the chemical transformations that occur in each reaction.

The commercially available 1,2 benzenedimethanol (**9**) is converted to the hydrazo compound **10** using phosgene and methyl carbazate in 69% yield. This material can also be obtained by phenyl chloroformate activation to give **11** followed by reaction with methyl carbazate. Although the activation by phenyl chloroformate proceeds in quantitative yield, reaction of **11** with methyl carbazate in presence of 4-dimethylaminopyridine (DMAP) is a very slow process (15 days) at 25 °C and gives a mixture of starting materials and products from which the purification of **10** is difficult. Thus, it appears that activation of the hydroxyl groups by phosgene is a more favourable approach. Oxidation of **10** by N-bromosuccinimide (NBS) and pyridine (pyr) according to standard procedures[51] gives compound **8** in 85% yield. This suggests that the sequence involving modification of a hydroxymethyl benzene moiety with phosgene and methyl carbazate could readily provide the required polymer-supported alkyl azodicarboxylate.

Hydroxymethyl polystyrene resins of light (**a** series) and heavy (**b** series) degrees of 'loading' of functional groups were examined. Hydroxymethyl polystyrene resin **12a** (0.55 mequiv/g, 5.8 mol% loading) is commercially available from Bachem. The use of a polystyrene which can be completely burned and is free of nitrogen enables the measurement of functionalization by elemental combustion analysis. In addition, the appearance or disappearance of bands in the infrared spectrum (IR-Fluorolube mull) allows further characterization of the polystyrene in each step of the chemical modification procedure.

The polystyrene more heavily loaded with hydroxymethyl groups **12b** (4.2 mequiv/g, 50 mol % loading), can be generated from commercially available chloromethyl polystyrene **13** (Merrifield peptide resin, Biobeads S-X1, 3.90 mequiv/g, 50.1 mol% loading)[12, 52] by a simple two step literature procedure[53] (Scheme 10). Reaction of the

Scheme 10.

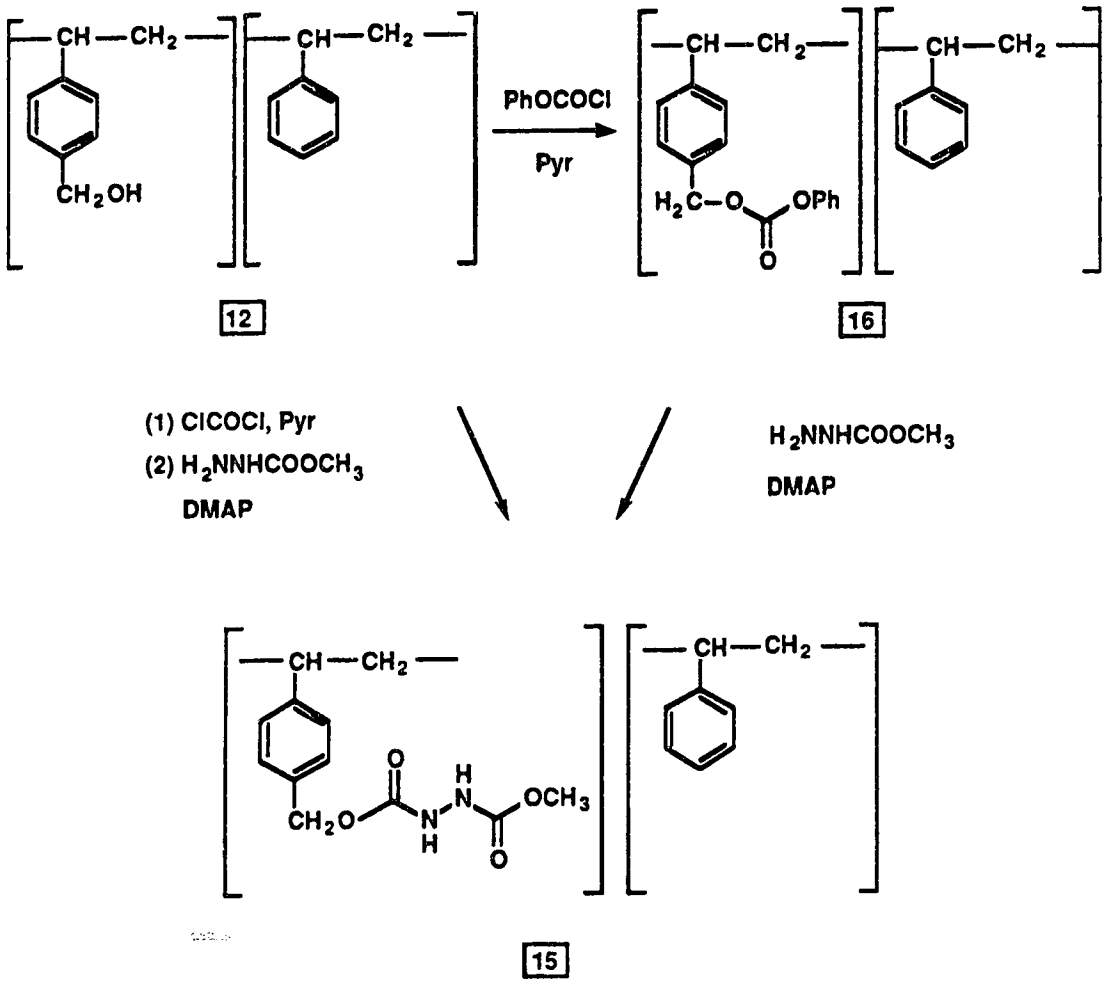


13 14 12b

chloromethyl polystyrene **13** with potassium acetate in dimethylacetamide at 80 °C for 28 h gives the acetoxymethyl resin **14** . The IR spectrum of **14** indicates the presence of the carbonyl band at 1736 cm^{-1}. Elemental analysis shows no detectable chlorine, thus confirming the quantitative conversion of the chloromethyl functional groups to acetoxymethyl groups. The hydroxymethyl polystyrene resin **12b** is obtained from **14** by reaction with anhydrous hydrazine in dimethylformamide at 20 °C for 24 h. Complete disappearance of the carbonyl band and appearance of the -OH band (3360 cm^{-1}) in the IR spectrum indicates quantitative conversion of the acetoxy groups to hydroxyl. The results of elemental analysis confirm this. Activation of the hydroxymethyl resin **12b** using phosgene and subsequent treatment with methyl carbazate in presence of triethylamine or 4-

dimethylaminopyridine affords the alkyl hydrazodicarboxylate resin **15b** (Scheme 11).[54, 55] Attempts to replace phosgene in these procedures with phenyl chloroformate gives the

Scheme 11.



(a) 5.8 mol% loading

(b) 50 mol% loading

polystyrene **16b** which also reacts with methyl carbazate to afford the alkyl hydrazodicarboxylate resin **15b**. However, the oxidized form of **15b** prepared through

this procedure performs only one cycle of Mitsunobu reactions and cannot be reliably recycled (see below) (Table 1). These observations coincide with those obtained with the

Table 1. Analysis of Polystyrene Resins.

Resin loading[1]	Method of Preparation[2]	%N Found Resin **15**	%N Found Resin **17**[3]
a	(i)	1.10	0.96
b	(i)	6.72	6.76
b	(ii)	6.40	6.13
b	(ii)	5.96	-
b	(ii)	5.70	3.41
b	(ii)	4.85	-

[1] **a** : 5.8 mol% loading, theoretical %N of **15** = 1.44, of **17** = 1.44; **b** : 50.1 mol% loading, theoretical %N of **15** = 7.96, of **17** = 7.96.

[2] (i) preparation through activation by phosgene, (ii) activation by phenyl chloroformate.

[3] Oxidized form of resin **15**.

soluble compound **8** where activation with phenyl chloroformate is slow and appears to cause undesirable side reactions. Since any side products that occur with the polymer cannot be separated, they would cause complications during the application or recycling of a polymer-supported reagent.

The lightly-loaded polystyrene resin **15a** (Scheme 11) is available from the hydroxymethyl resin **12a** by conversion to the corresponding chloroformate using phosgene[54] in presence of pyridine, and subsequent treatment with methyl carbazate and triethylamine.[55] Incorporation of the hydrazo functionality is evident from the very strong

carbonyl band in the IR spectrum (1790-1680 cm^{-1}). Elemental analysis is consistent with derivatization of 76% of the available hydroxymethyl groups (i.e., 0.40 mequiv/g, 4.4 mol % loading). Attempts to prepare **15a** by activation of the hydroxyl groups using phenyl chloroformate gave the phenyl carbonate form of the resin **16a**, but this did not react further with methyl carbazate to give **15a**. This is apparent from the fact that no nitrogen could be detected by elemental analysis of the resin even after prolonged reaction time (5 days). Such behaviour is comparable to that of the soluble model compound **9** where it was evident that the phenyl carbonate derivative **11** is not very reactive towards methyl carbazate.

Oxidation of the white methyl hydrazodicarboxylate resins **15a** and **15b** by a variety of oxidizing agents (Table 2) affords the corresponding yellow-orange

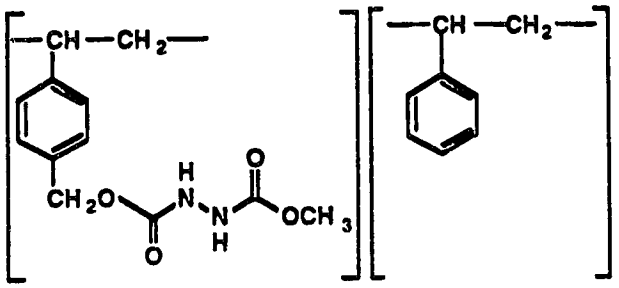
Table 2. Oxidation of Hydrazodicarboxylate Polystyrenes 15 to the Azo Forms 17.

Reactant Polystyrene 15*	Oxidizing Agent	Reaction Conditions	N Analysis (%) of 17	
			Theoretical	Found
b	Cl_2 (g)	CH_2Cl_2, 6 h, 20 °C	7.96	4.55
b	NBS	CH_2Cl_2, 1 h, 20 °C	7.96	6.76
a	NBS	CH_2Cl_2, 1 h, 20 °C	1.44	0.96
a	HOCl	THF/H_2O, 6 h, 5-10 °C	1.44	1.11
a	N_2O_4	CH_2Cl_2, 0.5 h, 0-20 °C	1.44	1.54

* **a** : 5.8 mol% loading, **b** : 50.1 mol% loading.

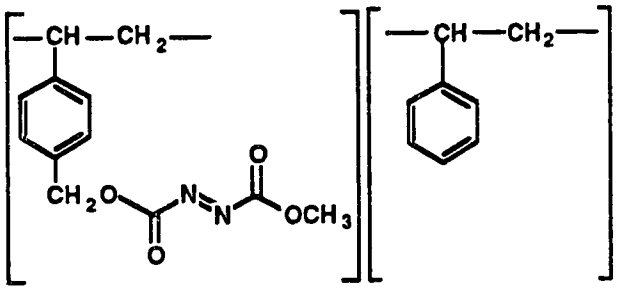
methylazodicarboxylates **17a** and **17b** respectively (Scheme 12). N-Bromosuccinimide (NBS) in presence of pyridine[51] is the most appropriate reagent since the polystyrene is easily oxidized under these conditions (1 h, 20 °C). Reaction "work-up" involves washing

Scheme 12.



15

OXIDATION



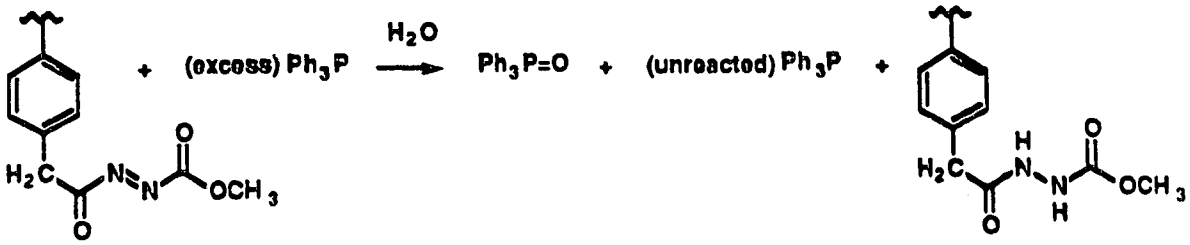
17

the polystyrene with acetonitrile, filtering, and drying *in vacuo*. Examination of the IR spectrum shows complete disappearance of the -NH peak (~3300 cm^{-1}). Nitrogen elemental analysis of the oxidized polystyrene is low, but this was found to be a general problem in nitrogen determinations on the azodicarboxylate polystyrenes **17**. This may be due to thermal decomposition leading to loss of nitrogen during the analysis. Soluble dialkyl azodicarboxylates are also oxidized by chlorine gas,[56] chlorine water[57] and nitrogen tetroxide.[58] The polystyrene hydrazodicarboxylate **15b** is oxidized by chlorine gas[56] in

dichloromethane at 25 °C. This is evident from the IR spectrum of the resulting polymer. However, elemental analysis shows a high percentage of chlorine, which indicates its possible incorporation on the aromatic residues in the polystyrene. This azodicarboxylate polymer is, however, reactive under Mitsunobu conditions and can be used for at least two cycles of oxidation/reduction reactions. Thus, the presence of the chlorophenyl residues in the polystyrene does not appear to have much effect on the reactivity of the azodicarboxylate moiety. Since the oxidation using chlorine gas needs 6 h for completion, it is less favourable than the reaction with NBS. Chlorine in presence of water (HOCl)[57] is effective in oxidizing the hydrazo moiety. In addition, no chlorine is detected in the resulting polymer by elemental analysis. However, the long reaction time needed (6 h) still makes this process less desirable. Oxidation using dinitrogen tetroxide (N_2O_4)[58] at 0 - 20 °C requires only 30 minutes. However, nitrogen elemental analysis is suspiciously high, especially since -NH peaks are still present in the IR, indicating incomplete oxidation. Since N_2O_4 is used for formation of N-nitroso compounds from amines[59] and aromatic nitro compounds from arenes,[60] it is possible that these unfavourable side reactions occur during oxidation of the hydrazo group.

In order to determine the concentration of accessible (i.e., synthetically usable) azodicarboxylate functionalities on the resin, the polystyrene derivative **17** is treated with a known amount of excess triphenylphosphine in dry tetrahydrofuran (THF), and the resulting adduct is quenched with excess water (Scheme 13). An amount of triphenylphosphine equal to the number of equivalents of azo groups available becomes oxidized to triphenylphosphine oxide which is isolated together with unconsumed excess triphenylphosphine. ^{1}H NMR analysis of the ratio of the recovered triphenylphosphine (δ 7.3) and triphenylphosphine oxide (δ 7.5) indicates the level of accessible azodicarboxylate units.

Scheme 13.



17

The accuracy of this method was tested in different ways. ^{1}H NMR spectra of control samples of triphenylphosphine and triphenylphosphine oxide, weighed and mixed to known molar ratios, give accurate results. To determine the possible influence of reaction time, a sample of the resin **17b** treated with triphenylphosphine for 30 minutes was quenched with water. The ^{1}H NMR indicates that 1.8 mequiv/g of accessible azo groups are available. This process was repeated on the recovered resin several times. The results (Table 3) show that after the first reduction, some azo groups are still available and

Table 3. Effect of Reaction Time on Accessible Azo Groups in 17b in Triphenylphosphine/Water Reaction.

	Accessible groups (mequiv/g) on Resin **17b** [a]		
Reaction	1[b]	2[c]	3[c]
(i)	1.8	2.0	1.9
(ii)	0.16	0.46	0.46
(iii)	0.035	-	-

[a] 50.1 mol% loading, theoretical value = 2.84 mequiv/g.

[b] Reaction time for each reaction : 0.75 h.

[c] Reaction time for each reaction : 24 h.

become accessible when the reduction is repeated. When the first reaction time is prolonged to 24 h, the number of accessible azo groups detected increases only slightly. It must, however, be noted that a sample of commercial triphenylphosphine in solution has been found to show increasing amounts of residual triphenylphosphine oxide if left for prolonged periods of time.

The polymer-supported reagent was also tested to determine if there is any adhesion of triphenylphosphine and/or triphenylphosphine oxide on the surface of the polystyrene. A sample of the hydrazodicarboxylate resin **15a** (before any oxidation) was mixed with a known ratio of triphenylphosphine and triphenylphosphine oxide (1 : 0.95), stirred for 30 minutes, and quenched with water. The recovered mixture of triphenylphosphine and triphenylphosphine oxide shows the same ratio (1 : 0.96) as the initial sample, within experimental error. Analysis of the recovered resin also indicates that no form of surface adhesion occurs between the phosphine mixture and the polystyrene resin.

The polymer-supported azodicarboxylate reagent **17b**, obtained by oxidation using N-bromosuccinimide in presence of pyridine, is recyclable for at least six cycles of oxidation/Mitsunobu reactions (reduction). In each cycle, a sample of the oxidized polystyrene was tested with the triphenylphosphine/water procedure to determine the amount of available active sites. The results (Table 4) are comparable to those obtained by analysis of peak intensities in the IR (Fluorolube mull) spectra. The latter involves comparison of the -NH band intensities (~3360 cm^{-1}) with those of the relatively constant C=C (2920 cm^{-1}) bands. This use of FT-IR as a semi-quantitative means of determination of the success of reactions on polymers is widely used.[7] However, this reflects the total amount of azo groups actually present, not all of which may be accessible for reaction due to steric bulk or insufficient swelling of the beads by the solvent. Thus, the triphenylphosphine/water test provides a more practical estimate of the number of usable azodicarboxylate units. Tetrahydrofuran is used for this determination and for the actual

Table 4. Accessible Azodicarboxylate Sites on Recycled Resins 17b.

Cycle	Available sites[1] (mequiv/g) based on IR[2]	Ph_3P/H_2O reaction	
1	2.47	2.13	(CD_3CN)[3]
2	1.87	1.65	$(CD_3CN$-DMSO $d_6)$
3	2.47	1.18	(CD_3OD)
4	2.49	1.82	(DMSO d_6)

[1] Value based on theoretical mol% loading = 2.84 mequiv/g.

[2] Based on ratio of $A_{3360/2920}$ bands in IR.

[3] Solvent for NMR analysis.

Mitsunobu reactions (discussed below) because of its great ability to cause swelling of the polymer beads[52, 61] and to dissolve most reagents.

Thus, chemical modification of the hydroxymethyl polystyrene **12** affords the polymer-supported alkyl hydrazodicarboxylate resin **15** in a straightforward two-step procedure, and direct oxidation gives the required alkyl azodicarboxylate polystyrene reagent **17** (Table 5). This sequence, originally examined in preliminary experiments by Dr. Lee Arnold,[19b] is short and has no detectable side reactions. All reactions can be performed in a jacketed reaction vessel containing a glass filter at the base.[19b] In this way, the polystyrene can react under dry conditions and be filtered, washed, and dried *in vacuo* without transfer to other containers. This minimizes loss of polymer beads and facilitates manipulations of the polystyrene. In addition, when the polymer is exposed to sudden and severe mechanical shock, no signs of any reaction is observed. Heating the polymer to 400

Table 5. Active Sites on Polystyrene Resins a and b.

Resin	12		15		17	
	mequiv/g[1]	mol%[1]	mequiv/g[2]	mol%[2]	mequiv/g[3]	mol%[3]
a	4.2	50.1	2.4	42.7	2.1	37.6
b	0.55	5.80	0.40	4.46	0.27	3.01

[1] Values based on analysis by commercial supplier.

[2] Hydrazodicarboxylate sites based on N elemental analysis.

[3] Accessible azodicarboxylate sites based on reaction with triphenylphosphine/water.

°C over 2 h only causes it to shrink and turn dark brown in colour. Thus, the polymeric reagent **17** has no tendency to explode or ignite, and hence appears to be ideally suited for replacement of soluble dialkyl azodicarboxylates on industrial scale.

B. APPLICATION OF POLYMER-SUPPORTED AZODICARBOXYLATES IN MITSUNOBU REACTIONS.

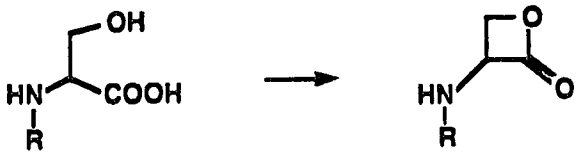
The importance and widespread use of the Mitsunobu reaction[27] renders the polymer-supported alkyl azodicarboxylate potentially valuable. It could be applied to synthesis of N-protected α-amino-β-lactones,[19] which provide an important route to synthesis of chiral α-amino acids. A large variety of other nucleophilic replacements of hydroxyl groups[27] could also be possible using the insoluble alkyl azodicarboxylate reagent, for example: carbon and nitrogen alkylation, and ester formations (including cyclization of hydroxy carboxylic acids). Even elimination reactions (e.g. desulfurization), which have been accomplished under Mitsunobu conditions could, in principle, be

performed in presence of the polymer-supported alkyl azodicarboxylate. In the present work, this polymer-supported reagent **17** is applied to selected examples of the above-mentioned reactions to examine its synthetic utility.

β-Lactone Formation and Synthesis of Diaminopimelic Acid Analogs.

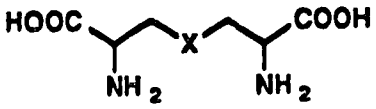
Recently, N-acylated serines **1** were cyclized under slightly modified Mitsunobu conditions to afford N-protected β-lactones **2** in good yields (60-72%) without racemization (Scheme 14).[19] Since serine (**1**, R = H) is readily available in

Scheme 14.



1 **2**

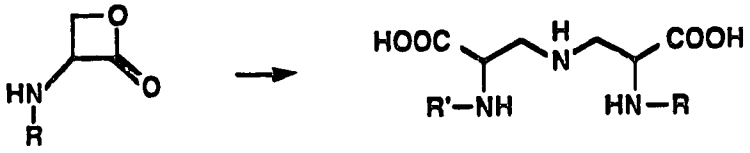
enantiomerically pure form at relatively low cost,[62] it is attractive as a chiral starting material.[63] The cyclization of N-protected serine to the corresponding β-lactone provides simultaneous protection of the carboxyl group and activation of the hydroxyl as a leaving group. Attack by a variety of heteroatom nucleophiles,[19, 21] produces β-substituted alanines which are biologically important.[64] Thus, large scale preparation of β-lactones would offer a synthetic route to industrial scale production of other amino acids in optically pure form. Among the amino acids accessible by this route are sulfur analogs of diaminopimelic acid. Compounds like lanthionine, its sulfoxide and its sulfone are competitive inhibitors of the diaminopimelate decarboxylase and epimerase enzymes.[18] Hence, preparation of other analogs is of interest. Derivatives in which the central methylene in diaminopimelic acid is replaced by nitrogen also possess a site for attachment to affinity column supports. It seems reasonable that such compounds could be prepared by



2,6-Diaminopimelic Acid	**X=CH_2**
Lanthionine	**X=S**
Lanthionine Sulfoxide	**X=SO**
Lanthionine Sulfone	**X=SO_2**

nucleophilic opening of the N-protected serine β-lactone **2** by a suitable alkylamine to give diaminopimelic acid analogs **18** or **19** (Scheme 15).

Scheme 15.

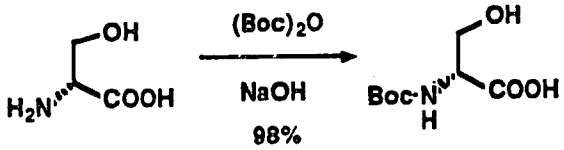


2 **18** **R=R'=Boc**

19 **R'=Cbz, R=Boc**

Commercially available D-serine reacts with di-*tert*-butyl pyrocarbonate to give N-(*tert*-butoxycarbonyl)-D-serine (**1a**) according to the general procedure of Moroder et al.[65] (Scheme 16). The corresponding L-isomer **1b** can be obtained commercially (Sigma).

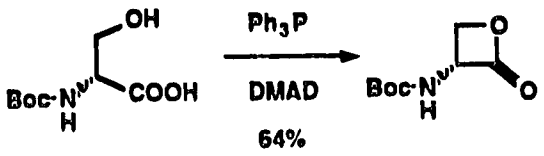
Scheme 16.



D-Serine **1a**

These N-protected serines react with dimethyl azodicarboxylate and triphenylphosphine at - 58 °C to give the corresponding β-lactones **2** in 61-64% yields (Scheme 17).[19]

Scheme 17.

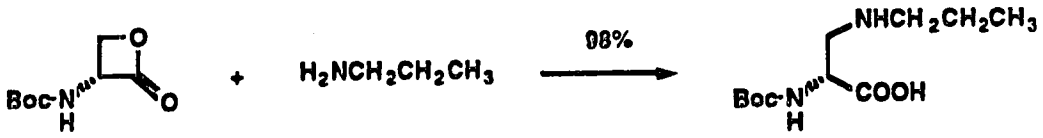


1a **2a**

To prepare the lactone **2b** in presence of the polystyrene-supported reagent **17a**, the polymer is swollen briefly (5 minutes) in THF at -45 °C and the N-protected serine **1b** and triphenylphosphine are added consecutively as solutions in dry THF. The temperature is raised slowly to 25 °C over 3 h. Twelve hours are needed for complete reaction (as indicated by TLC on the supernatant) of the starting material **1b**, and the lactone **2b** is isolated in 50% yield. Since only 1.2 equivalents of **17a** are employed, presence of excess of **17a** is likely to lead to increase in the yield of the lactone. Preliminary tests by Arnold[19b] indicate that preformation of the adduct between the polymer-supported azodicarboxylate and triphenylphosphine does not result in significant increase in yields of the isolated product, probably due to more significant losses to moisture. He was also able to simplify the purification process by precipitation of triphenylphosphine oxide from ether followed by recrystallization of the lactone from chloroform/carbon tetrachloride/hexane. This is an alternative method to the use of flash chromatography, and would be more favourable in industrial scale applications.

n-Propylamine opens the lactone ring to give N'-propyl-N-(*tert*-butoxycarbonyl)-L-2,3-diaminopropionic acid (**20**) in quantitative yield (Scheme 18), thereby demonstrating the ease of attack on the β-lactone by amines.

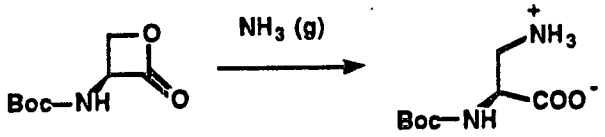
Scheme 18.



2a **20**

Similarly, ammonia[19] attacks the lactone **2a** or **2b** to afford N-(*tert*-butoxycarbonyl)-D-2,3-diaminopropionic acid (**21a**) or its L-isomer (**21b**) in 74 and 81% yields, respectively (Scheme 19). Compound **21** is a constituent of antibiotic and antitumor peptides[66] and may be used as a precursor to the diaminopimelic acid analogs **18** and **19** if it can attack the lactone in the same fashion as n-propylamine.

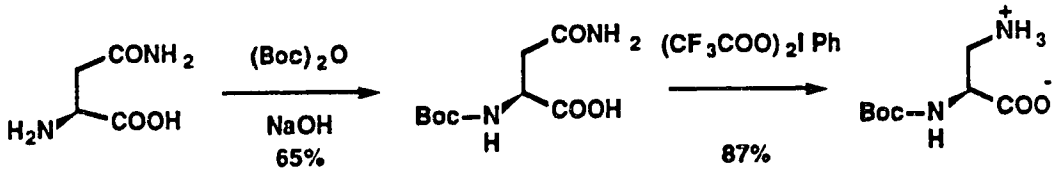
Scheme 19.



2b **21b**

To confirm its structure, compound **21b** was also prepared from N-(*tert*-butoxycarbonyl)-L-asparagine (**22**) using the method by Waki et al.[67] (Scheme 20). Compound **22** is commercially available or can be readily prepared from L-asparagine. It reacts with

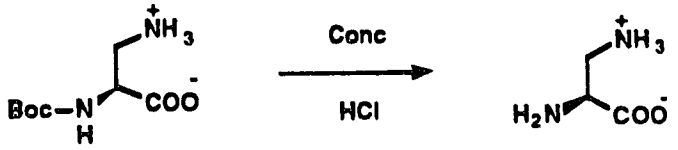
Scheme 20.



L-Asparagine **22** **21b**

[bis(trifluoroacetoxy)iodo]benzene to afford **21b** in 87% yield. This material is identical to that prepared from the β-lactone **2b**. Deprotection of **21b** gives 2,3-diaminopropionic acid (**23**) (Scheme 21) with NMR, IR and mass spectral properties identical to those of an authentic sample obtained from Sigma.

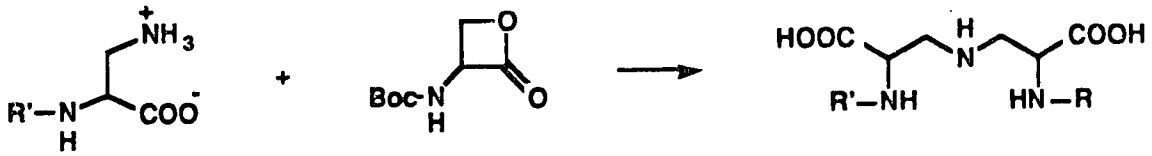
Scheme 21.



21b **23**

Since the lactone ring is obviously prone to attack by amine nucleophiles, the synthesis of the diaminopimelic acid analogs **18** and **19** was attempted using a similar approach (Scheme 22). However, when the β-lactone **2b** is added to **21a** in presence of triethylamine in THF, no product is observed even at temperatures as high as 60 °C,

Scheme 22.



21a R'=Boc (R) **2a: (R)** **18** R=R'=Boc

24 R'=Cbz (S) **2b: (S)** **19** R=Boc, R'=Cbz.

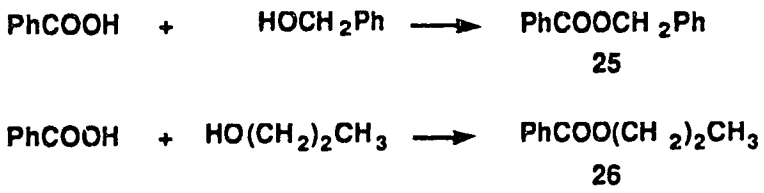
at which the β-lactone begins to decompose, and the starting materials are recovered. Potassium hydride was then chosen to replace triethylamine as the base. Reaction of the potassium salt of **21a** with **2a** in THF at 0 °C provides compound **18** in 3% yield with

almost quantitative recovery of the remaining amino acid **21a**. Since this lack of reactivity could be due to strong complexation between the amino group in **21a** with the potassium ion (K^+), the use of crown ether appeared to be the ideal solution. However, reaction of **24** with **2b** in presence of potassium hydride and 18-crown-6 at 25 °C affords the product **19** in only 1% yield. This decrease in yield probably occurs because of difficulties in purification of the product **19** from crown ether. In any case, the synthesis of these analogs by this route is more difficult than would be originally anticipated. Although the β-lactones are very easily attacked by nucleophiles, it appears that the amines **21** and **24** are not very reactive. This may be due to their zwitterionic character and possible tendency to complex to metals, like potassium ion.

Intermolecular Ester Formation.

The Mitsunobu reaction of an alcohol and a carboxylic acid[69] is an effective and popular method for intermolecular ester formation.[68] For example, benzyl benzoate (**25**) and n-propyl benzoate (**26**) can be prepared under Mitsunobu conditions (Scheme 23).

Scheme 23.



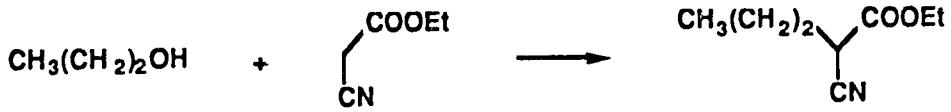
Using the soluble dimethyl azodicarboxylate reagent, benzoic acid reacts with benzyl alcohol[69a] in THF at 25 °C to afford the ester **25** in 82% yield. This reaction also proceeds with the insoluble polystyrene resin. The polymer **17b** (1.2 equivalents) is swollen in THF at room temperature and a solution of triphenylphosphine, benzoic acid and benzyl alcohol in THF is added. Reaction at 25 °C for 20 h affords **25** in 61% yield. Similarly,

esterification of benzoic acid using n-propanol[69b] proceeds in 56% yield in presence of the soluble reagent, and in 55% yield when the polymer-supported reagent **17a** (1.0 equiv) is utilized. Thus, yields obtained using the resin are favourably comparable to those obtained with the soluble reagent.

C-Alkylation.

The Mitsunobu reaction is synthetically useful in alkylation of active methylene groups in 30-80% yields.[41] In particular, n-propanol is known to react with ethyl cyanoacetate (**27**) in the presence of diethyl azodicarboxylate and triphenylphosphine to afford ethyl 2-cyanopentanoate (**28**) in 52% yield.[41] In presence of the polymer-bound azodicarboxylate **17a**, ethyl cyanoacetate (**27**) reacts with n-propanol in THF at 20 °C to afford compound **28** in 42% yield (Scheme 24). Since this yield is not optimized and only one equivalent of the polymer **17a** is used, it is an indication that the polymer-supported reagent is quite efficient in carbon-alkylations.

Scheme 24.

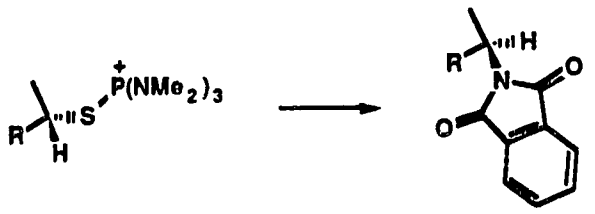


27 **28**

N-Alkylation.

N-Alkyl phthalimides are usually prepared by initial conversion of phthalimide to its conjugate base followed by attack on an alkyl halide.[71] Recently,[71b] chiral N-alkyl phthalimides have been prepared by attack of the conjugate base of the phthalimide on the adduct **G** (Scheme 25) in 79-83% yields. This reaction proceeds with inversion of configuration and is, therefore, a possible route to synthesis of chiral amines. Another

Scheme 25.

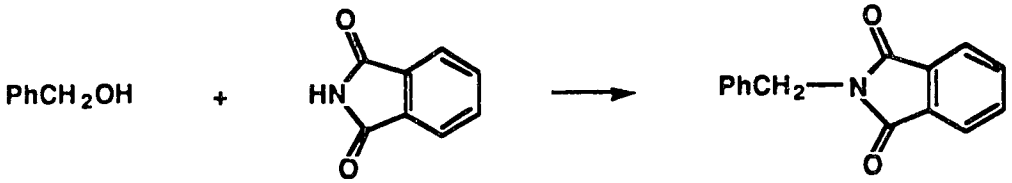


G

approach to preparation of N-substituted phthalimides was reported by Garcia et al.[72] This is performed as a 'one pot reaction' between azides and phthalic anhydride. It results in quantitative yields and chiral centers in the molecule remain unaltered. N-Alkylation, using the Mitsunobu conditions,[42] proceeds with inversion of configuration on the carbinol carbon. This renders it useful in the stereospecific synthesis of N-alkyl phthalimido compounds and esters of N-phthaloyl-α-amino acids.

Reaction of phthalimide with benzyl alcohol using the polystyrene azodicarboxylate **17a** (1.0 equivalents) at 25 °C in THF gives N-benzyl phthalimide (**29**) in 57% yield (Scheme 26). This is comparable to the literature[42] yield of 75% obtained with the soluble azodicarboxylate.

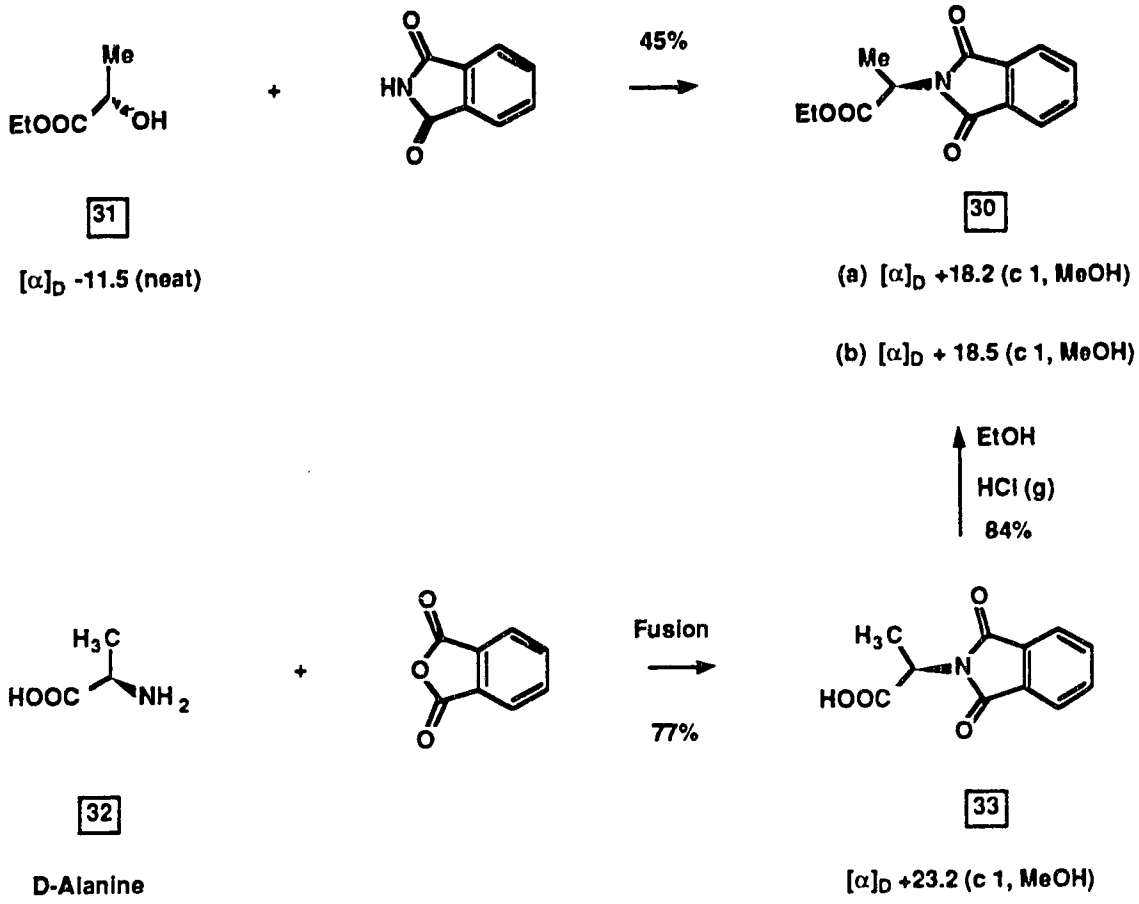
Scheme 26.



29

N-Phthaloyl-D-alanine ethyl ester (**30**) ([α]$_D$ +18.2 c 1, MeOH) can be prepared in a similar procedure from (S)-(-)-ethyl lactate (**31**), using the polymeric reagent **17b** (1.3 equivalents), in 45% yield (Scheme 27). In addition, 12% of initial phthalimide was

Scheme 27.



recovered, indicating that excess of the polystyrene reagent **17b** and triphenylphosphine are needed to increase the yield of **30**. An independent synthesis of **30**, which does not involve inversion of configuration, was done to confirm the stereochemical purity of **30** obtained using the polystyrene-supported reagent. D-Alanine (**32**) reacts with phthalic anhydride[73] to give N-phthaloyl-D-alanine (**33**) in 77% yield. Esterification of this

proceeds under acidic conditions with ethanol using standard conditions.[42] The resulting N-phthaloyl-D-alanine ethyl ester (**30**) (84% yield) has $[\alpha]_D$ +18.5 c 1, MeOH, identical, within experimental error, to **30** obtained using polystyrene resin **17b**. These results confirm that the reaction of **31** with phthalic anhydride proceeds with clean inversion of configuration, as expected in Mitsunobu reactions.

Desulfurization.

Carbodiimides are important precursors in nucleotide and peptide synthesis.[74] They are employed both in soluble form and as immobilized reagents on solid supports in preparation of ketones and aldehydes.[75] Carbodiimides are usually prepared by dehydrosulfurization or dehydration of thioureas or ureas.[74]

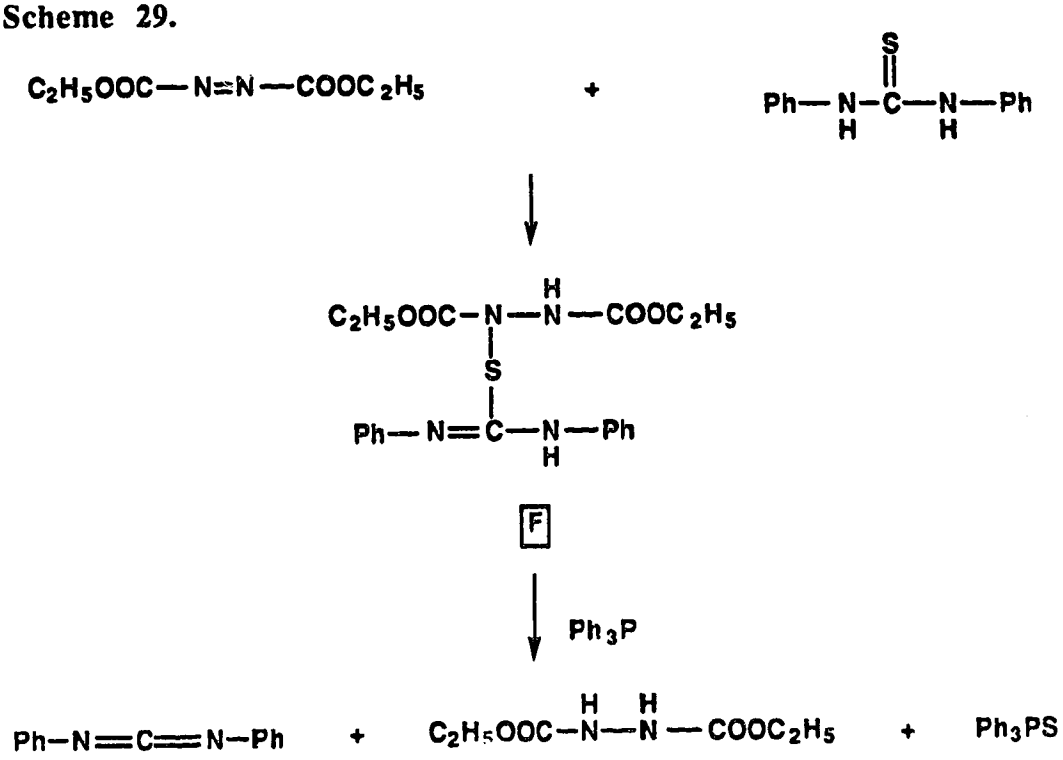
Dehydrosulfurization of thioamides under Mitsunobu conditions affords nitriles[43] and ketenimines.[44] Similarly, thioureas are converted to carbodiimides.[45, 46] The N,N'-diphenylthiourea (**34**) is reported to react with triphenylphosphine and the soluble alkyl azodicarboxylate to give the diphenyl carbodiimide (**35**) in 79% yield.[45] Using the azodicarboxylate polystyrene resin **17b** (1.1 equivalent) in THF at 20 °C, the carbodiimide **35** is prepared in 41% yield (Scheme 28).

Scheme 28.

34 **35**

These reactions are reported[45] to proceed through the intermediate **F** (Scheme 29).

Scheme 29.



In our hands, attempts to convert primary thioamides to nitriles (Scheme 30) fail to provide the required product even when the soluble dimethyl azodicarboxylate reagent is employed under conditions described in the literature.[43]

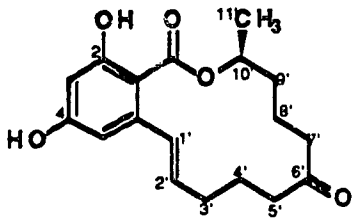
Scheme 30.

However, the polymer-supported alkyl azodicarboxylate appears to be effective in performing the elimination reactions that occur with the soluble reagent. It is, therefore, possible that similar desulfurization of thioamides to afford ketenimines could be performed using the polystyrene **17**.

Macrolactonization.

In general, it can be difficult to effect lactonizations when the hydroxyl and carboxyl groups are remote (separated by more than five carbons). However, such cyclizations have been widely investigated[76] and provide important synthetic routes to various macrolide antibiotics.[28,76-78]

Zearalenone (**36**) is an interesting macrocyclic compound[79] isolated in 1962 from the fungus *Gibberella zea* .[80] It has estrogenic effects[81,82] and a narrow range of



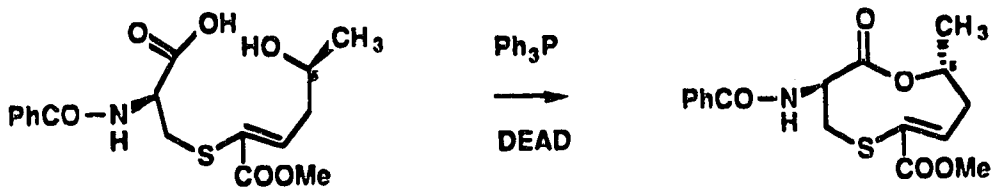
Zearalenone

antibacterial activity.[83] Several methods allow cyclization of the 14-membered ring in zearalenone as its dimethyl ether. Masamune[77] and Corey[78] used different thioesters of the hydroxy acid to effect the cyclization in 90% and 75% yields, respectively. Taub[84] and Peters[85] used trifluoroacetic anhydride (80% and 19% yields, respectively) while Vlattas et al.[86] prepared the methyl ester of the acid and cyclized the ring in presence of sodium and t-amyl alcohol in 8% yield. Others[87] prepared the macrolactone from precursors with intact ester linkage by cyclization at positions other than the lactone carbonyl.

None of the methods mentioned proceed by inversion of configuration at the carbon bearing the hydroxyl group. The Mitsunobu macrolactonization process, which involves inversion of stereochemistry, is, therefore, extremely useful in syntheses where a different stereoisomer is the target. The Mitsunobu reaction conditions have been used for

macrolactonizations leading to the preparation of several important antibiotics.[28] Meyers et al.[28a] used this approach to prepare the macrolactone **J** (Scheme 31) as a precursor of the

Scheme 31.



K **J**

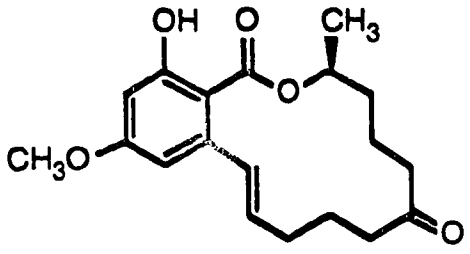
antibiotic griseoviridin. The hydroxy acid **K** was prepared stereospecifically with S configuration at C-5. Lactonization with triphenylphosphine and diethyl azodicarboxylate (DEAD) gives **J** in 47% yield, with inversion of stereochemistry at C-5.

To test the polystyrene-supported reagent **17** in Mitsunobu macrolactonizations and compare its effectiveness with the soluble alkyl azodicarboxylate, zearalenone (**36**) lactonization was examined. Protection of the phenolic hydroxyl groups appears necessary to avoid complications. This was accomplished by heating **36** with dimethyl sulfate and potassium carbonate in acetone at 54 °C for 1.5 h.[84] The monomethyl ether **37** and the required dimethyl ether **38** were obtained in 21% and 35% yields, respectively. Increasing the reaction time to 3 h gives only **38** in 85% yield (Scheme 32). The ^{1}H and ^{13}C chemical shift assignments of the monomethyl ether **37** (Table 6) are based on homonuclear proton decouplings, proton COSY (Fig. 2), ^{1}H-^{13}C heteronuclear shift correlation (Fig. 3) and NOE experiments. The monomethyl ether **37** has the methoxy group at C-4. This is verified by the proton NMR chemical shift of the hydroxyl proton, which is characteristic of phenolic -OH hydrogen bonded to an α-carbonyl, and NOE experiments. Irradiation of

Table 6. **^{13}C and ^{1}H NMR Chemical Shift Assignments for Zearalenone Monomethyl Ether 37 and Dimethyl Ether 38 In $CDCl_3$.**

Carbon	δ ^{13}C*		δ ^{1}H*	
No.	**37**	**38**	**37**	**38**
1	103.63	116.44	-	-
2	164.07	157.75	12.11 (-OH)	-
3	106.19	101.39	6.40	6.61
4	165.66	161.36	-	-
5	99.99	97.79	6.47	6.35
6	143.36	136.66	-	-
1'	133.31	129.06	7.02	6.39
2'	132.36	133.22	5.70	6.00
3'	31.02	31.26	2.18, 2.38	2.11, 2.35
4'	21.06	21.63	1.66, 2.18	1.60, 2.15
5'	36.66	37.64	2.86, 2.18	2.11, 2.71
6'	210.95	211.36	-	-
7'	42.97	44.09	2.62, 2.18	2.35
8'	22.26	21.33	1.77	1.81
9'	34.77	35.20	1.70	1.72
10'	73.41	71.19	5.02	5.30
11'	20.66	20.07	1.40	1.34
12'	171.42	167.61	-	-
C_2-OCH_3	-	56.01	-	3.80
C_4-OCH_3	55.42	55.46	3.85	3.85

*ppm from Me_4Si.



37

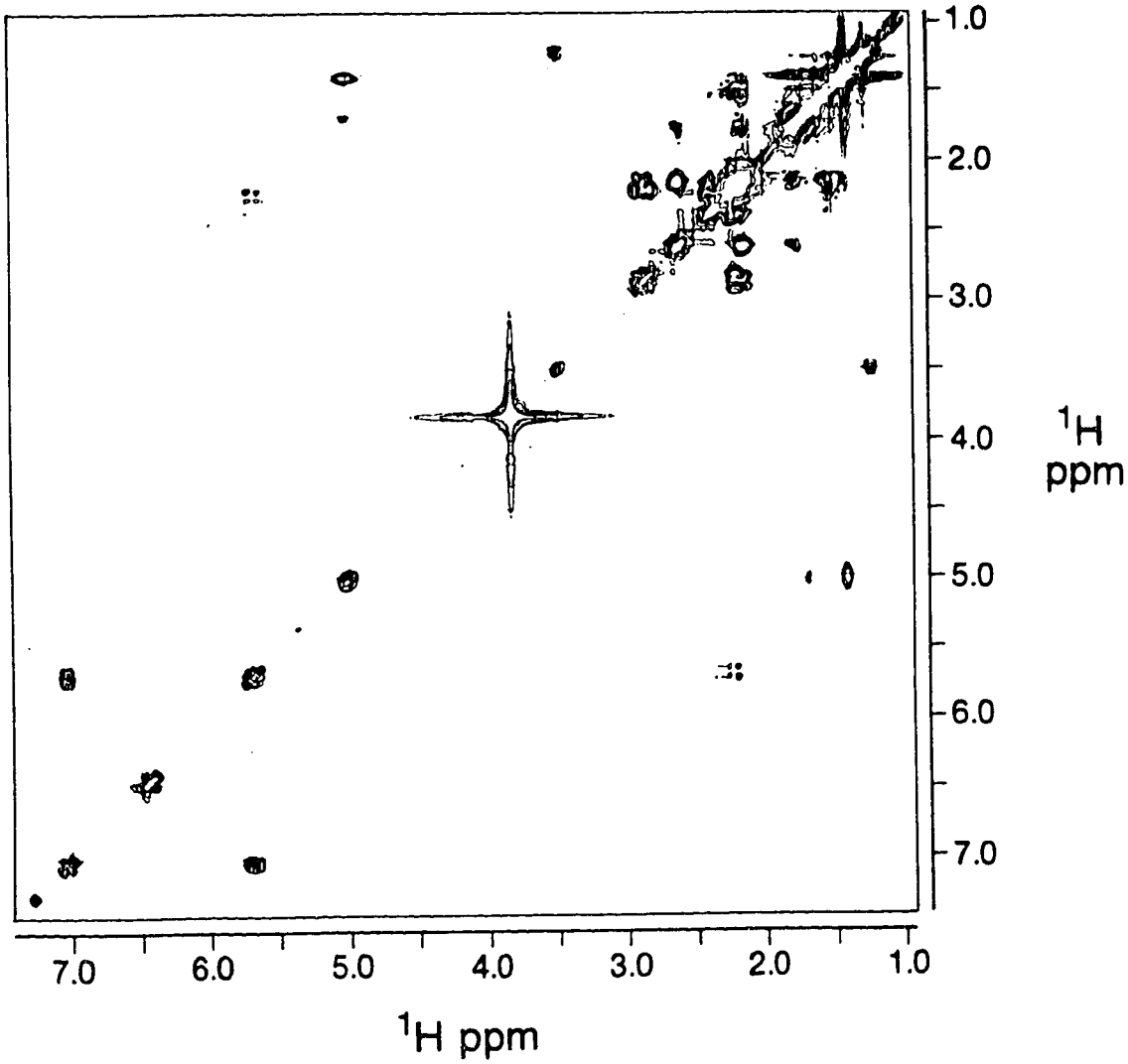


Fig. 2. ^{1}H-^{1}H COSY for Zearalenone Monomethyl Ether 37.

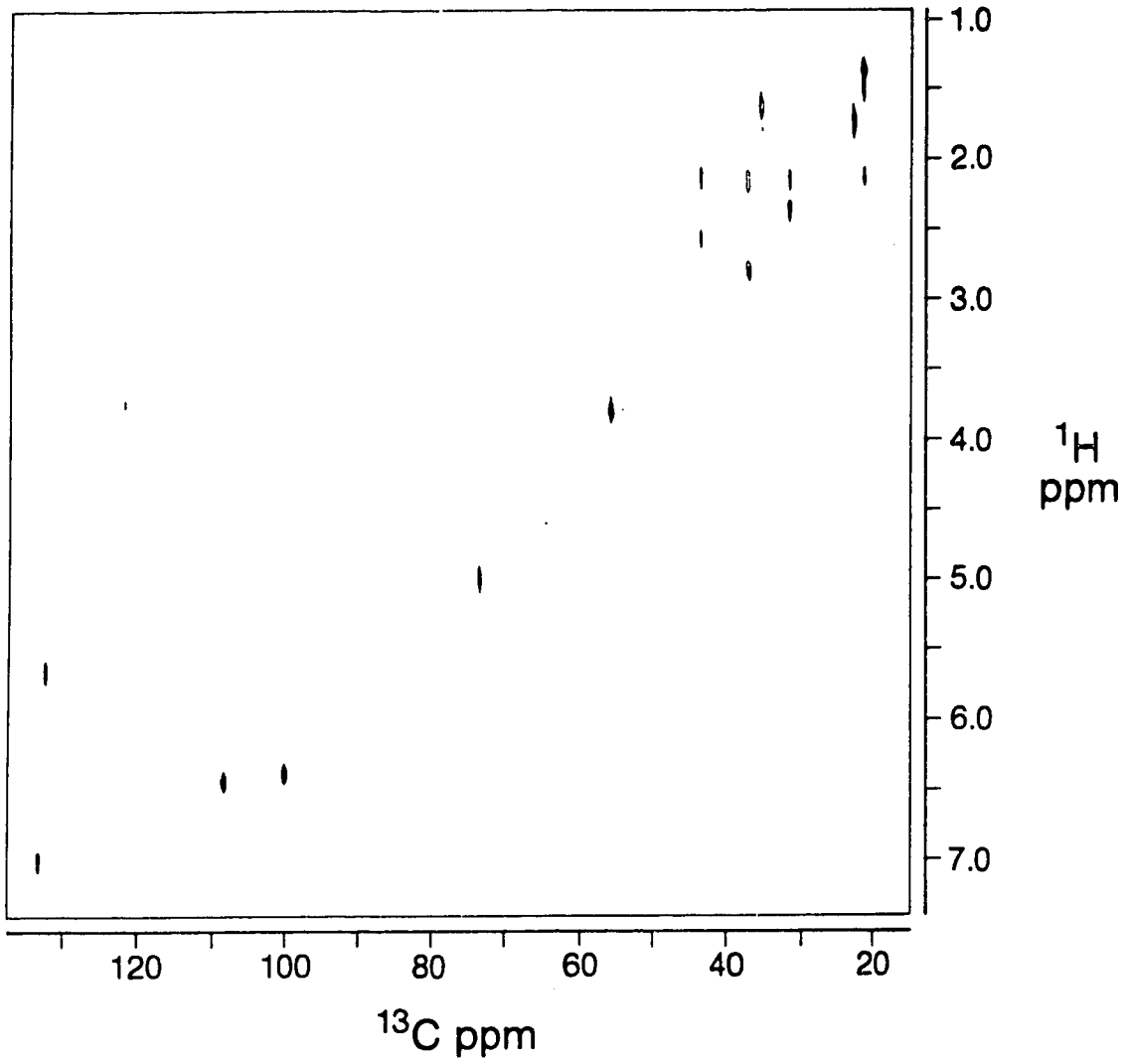
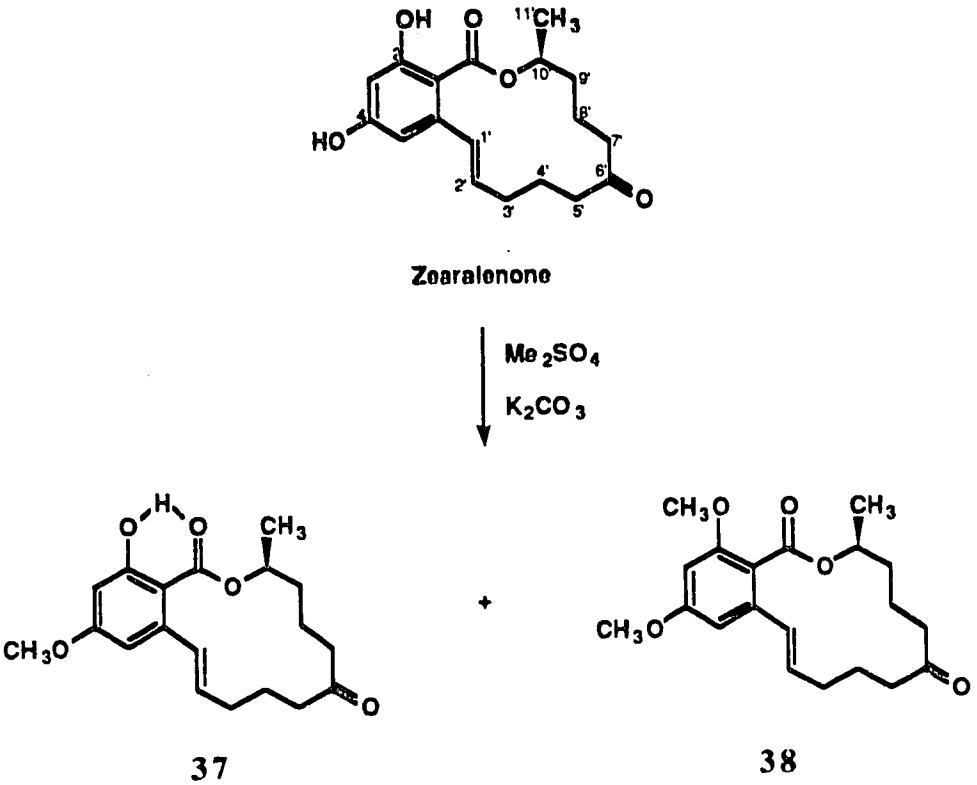


Fig. 3. **^{1}H-^{13}C NMR Heteronuclear Shift Correlation for Zearalenone Monomethyl Ether 37.**

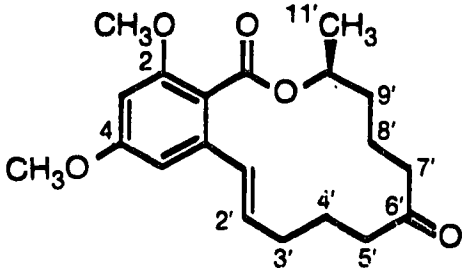
the hydroxyl proton enhances only the signal for the proton at 3-C whereas irradiation of the -OCH_3 protons enhances two signals (3-H and 5-H). The 3-H resonance is assigned

Scheme 32.



based on its NOE on both the hydroxyl and the methoxy protons. The identification of 5-H is based on its NOE on 2'-H. Homonuclear proton decouplings of 2'-H enhances protons at 3'-C, which in turn couple to those at 4'-C and 5'-C. The unique methyl doublet at δ 1.40 is assigned to the 11'-CH_3 protons. Homonuclear decoupling of this signal identifies 10'-H and hence 9'-H. Further proton decouplings assign 8'-C and 7'-C proton signals. These results are in agreement with the ^1H-^{13}C correlation shown in Fig. 3 and the ^1H-^1H correlation in Fig. 2.

Assignment of ^1H and ^{13}C NMR chemical shifts for zearalenone dimethyl ether **38** (Table 6) are based on ^1H-^{13}C heteronuclear correlation (Fig. 4) and homonuclear proton



38

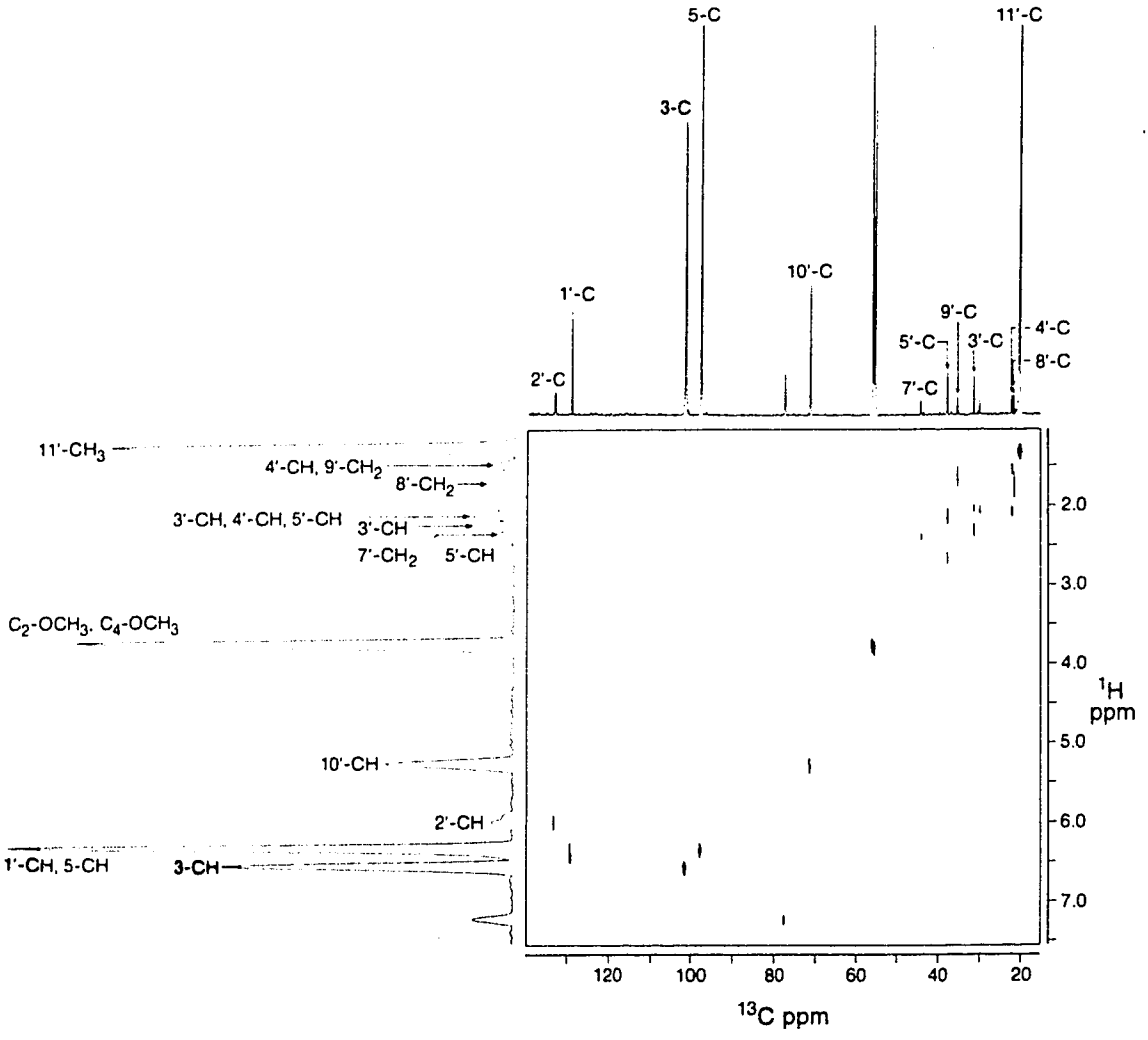
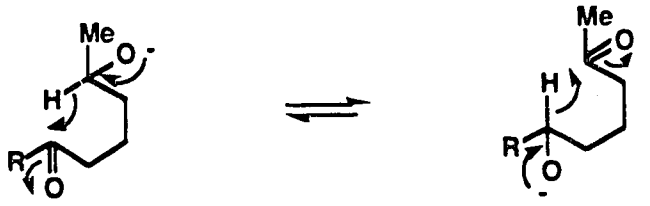


Fig. 4. **^{1}H-^{13}C NMR Heteronuclear Shift Correlation for Zearalenone Dimethyl Ether 38.**

decouplings. Figure 4 indicates that three of the methylene carbons in the dimethyl ether **38** have diastereotopic protons that appear at quite different chemical shifts in the ^{1}H NMR spectrum, in contrast to an earlier literature assignment.[81] Homonuclear decoupling experiments, similar to those performed on the monomethyl ether **37**, confirm the positions of the methylene proton signals. Carbon and proton chemical shifts of 3-C and 5-C agree with literature[88] assignments of zearalenone.

Taub et al.[84] had found that direct hydrolysis (aqueous NaOH, DMSO, 120 °C, 2 h) of the lactone ring in zearalenone dimethyl ether **38** causes racemization. They suggested that this is due to the position of the ketonic carbonyl and occurs through internal disproportionation to form the intermediate **39** (Scheme 33).

Scheme 33.

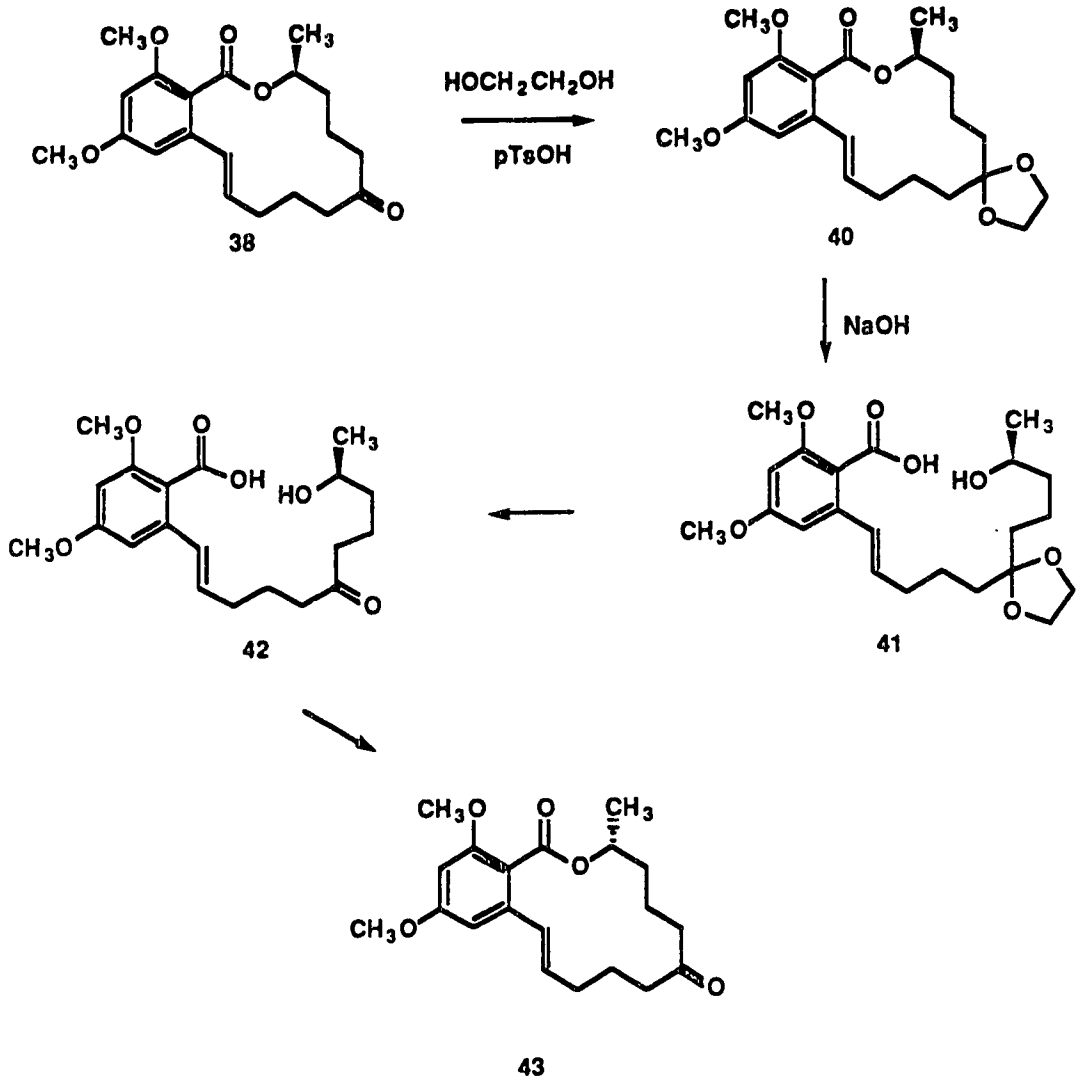


39

They were able to avoid this problem by protection of the carbonyl before hydrolysis. The dimethyl ether **38** ($[\alpha]_D$ = +23, c 1 MeOH) was, therefore, converted into the ethylene ketal **40** and hydrolyzed using the literature procedure[84] (Scheme 34) to afford **41** (95% yield). Deprotection by acid treatment (perchloric acid, 25 °C, 2 h) gives **42** in quantitative yield. Lactonization of **42** using the azodicarboxylate polystyrene resin **17b** (1.7 equivalents) at 25 °C in THF affords the dimethyl ether **43** in 42% yield with a stereochemistry ($[\alpha]_D$ = -23, c 1 MeOH) opposite to that of the initial dimethyl ether **38**. The lactonization of **42** (in its racemic form), when performed in presence of soluble

dimethyl azodicarboxylate, results in only 13% yield. Thus, the polymeric reagent is a useful tool in macrolactonizations.

Scheme 34.



Conclusion.

In summary, polymer-supported alkyl azodicarboxylates were synthesized. Functionalization of silica gel using 1,5-difluoro-2,4-dinitro-benzene was not successful. However, silica gel is still an attractive option for use as a solid support for the reagent, and other means of functionalization and linking arms may be explored.

Polystyrene proved to be a good support matrix for the reagent. It is functionalized in very few steps from commercially available hydroxymethyl or chloromethyl polystyrenes, and performs well in Mitsunobu reactions of different kinds (Table 7).

Table 7. Reactions Using Soluble And Polymer-Supported Azodicarboxylates.

Entry	Product	% Yield	
		DMAD/DEAD[1]	Resin **17**
1	N-(*tert*-butoxycarbonyl)-α-amino-β-propio-lactone (**2**)	81[2]	50
2	Benzyl Benzoate (**25**)	82[3]	61
3	n-Propyl Benzoate (**26**)	56[3]	55
4	Ethyl 2-Cyanopentanoate (**27**)	51[4]	42
5	N-Benzyl Phthalimide (**29**)	75[5]	57
6	N-Phthaloyl-D-Alanine Ethyl Ester (**30**)	58[5]	45
7	N,N'-Diphenyl Carbodiimide (**35**)	79[6]	41
8	(R)-(-)-Zearalenone Dimethyl Ether (**43**)	13[7]	42

[1] DMAD = Dimethyl azodicarboxylate, DEAD = Diethyl azodicarboxylate

[2] Ref. 19. [3] Our Yields. [4] Ref. 41. [5] Ref. 42. [6] Ref. 45.

[7] Typical yields for Mitsunobu macrolactonization = 8 - 63% (Ref. 28)

O-alkylation of oximes[89] was also attempted, using benzophenone oxime (**44**), but no alkylated product was obtained even when the soluble reagent is used.

Reaction conditions are not optimized. Tetrahydrofuran, which was used as the solvent in all cases, has a high ability to swell the polymer beads, but so do other solvents

(e.g. dichloromethane). Varying the solvent and/or temperatures may result in determination of the ideal conditions for each transformation. The reactions described here were all performed using 1.0-1.7 equivalents of **17** and triphenylphosphine except the C-alkylation where 3.4 equivalents were used. In some cases, as in the preparation of N-phthaloyl-D-alanine ethyl ester (**30**), starting materials were recovered. Thus, it is quite likely that yields obtained here with the polymer-supported reagent may be increased by use of a larger excess of the reagents. This will not cause problems in purification since any excess adduct between the azodicarboxylate and triphenylphosphine may be quenched with water when reaction is complete. The polymer is separated by filtration and the by-product triphenylphosphine oxide can, in many cases, (e.g. formation of β-lactone **2**) be separated by crystallization.[19b] In addition, the polymer-bound azodicarboxylate is not explosive and can be recycled. It, therefore, overcomes the disadvantages of using the soluble reagent on industrial scale.

EXPERIMENTAL

General

Hydroxymethyl polystyrene resin (0.55 mequiv/g, 1% cross-linked with divinylbenzene) was obtained from Bachem Inc. and chloromethylated polystyrene resin (3.90 mequiv/g, 1% crosslink, Bio-Beads S-X1) was from BioRad Laboratories. Reactions involving the polystyrene were performed in a jacketed reaction vessel equipped with a sintered glass filter and vacuum outlet/argon inlet at its base.[19b] To avoid loss of polymer beads due to adhesion to glass, all apparatus used was pretreated with a 10% solution of Surfasil siliconizing agent (Pierce) in hexane and oven dried overnight at 140 °C. All reactions in presence of the polystyrene were performed under a positive pressure of argon. This is replaced by vacuum during filtration of the polymer. The polystyrene beads were stirred gently (50-140 rpm) to avoid mechanical destruction. After each reaction, the resin was washed by suspending in an appropriate solvent, stirring for ~15 minutes, and then filtering under vacuum. It was then dried in the same container by applying vacuum and placing water in the outer glass jacket heated with a thermostatted coil.

All solid compounds were dried under vacuum over phosphorous pentoxide (P_2O_5) for 24 h prior to use. Solvents and liquid reagents were dried under argon according to Perrin et al.[90]: Tetrahydrofuran (THF) was distilled from Na/benzophenone; acetonitrile (CH_3CN), dichloromethane, benzyl alcohol, n-propyl alcohol, triethylamine (Et_3N) and pyridine were distilled from calcium hydride; dimethylformamide (DMF) and ethyl ether were obtained commercially as anhydrous reagents. n-Propylamine was distilled under argon at atmospheric pressure (bp 48 °C). Acetone was dried over potassium carbonate and distilled under atmospheric pressure (bp 54 °C). All solvents used in chromatographic purification were distilled.

N-Bromosuccinimide (NBS) was recrystallized from water, dried under vacuum over P_2O_5 and stored in the dark. Commercial dimethyl azodicarboxylate was distilled (safety shield, explosion hazard)[33] under reduced pressure before use (bp 71-72 °C at 2 mm Hg). Succinic anhydride was recrystallized from distilled acetic anhydride, filtered, washed with ether and dried under vacuum. Crown ether (18-crown-6) was recrystallized from ether and dried under vacuum. All other reagents were obtained commercially and used without further purification.

Infrared spectroscopy was measured on a Nicolet 7199 FT-IR spectrometer. Only peaks above 1500 cm^{-1} are reported. Microanalyses were obtained using a Perkin Elmer 240 CHN analyzer. Nuclear magnetic resonance (NMR) spectra were measured on Bruker WP-80 (CW), WH-200, AM-300, WM-360 or WH-400 instruments. Tetramethylsilane was used as the internal standard, unless otherwise mentioned. Mass spectra (MS) were obtained using a Kratos AEI MS-50 (high resolution, electron impact ionization) for exact mass determinations, MS-12 for chemical ionization (CI MS), and MS-9 for fast-atom bombardment with argon (POSFAB MS). Melting points (mp) were determined on a Thomas Hoover oil immersion apparatus in open-end capillary tubes and are uncorrected. Optical rotations were measured on a Perkin Elmer 2412 polarimeter with a microcell (10 cm, 2 mL) at ambient temperature (25 ± 2 °C).

Thin-layer chromatography (TLC) was used to determine the extent of reactions where possible. Spots were visualized using UV absorption or I_2 staining where applicable. Bromocresol green spray (0.04% in ethanol, made blue by NaOH) was used for visualization of acids while ninhydrin spray was used for amino acids. Commercial thin-layer chromatography (TLC) plates used were silica (Merck 60F-254) or reverse-phase (Merck RP-8 F254 S). Reverse phase medium pressure liquid chromatography (MPLC) was performed using two Merck Lobar Lichroprep RP-8 columns (size A and B) in series. Flash chromatography was performed according to Still et al.[91] using Merck type 60, 230-420 mesh silica gel.

All operations involving phosgene were conducted in an efficient hood with special precautions due to the toxicity of the gas. The concentration of the toxic gas present in the hood was detected using paper soaked in 10% solution of p-dimethylaminobenzaldehyde and diphenylamine (1 : 1) in 95% ethanol. All filtrates/solutions were treated with aqueous ammonia in the hood, to destroy excess phosgene, before they were discarded.[92]

N-(*tert*-Butoxycarbonyl)-D-Serine (1a).

The general procedure of Moroder et al.[65] was adopted. D-Serine (2.01 g, 19.2 mmol) was dissolved in dioxane/water (2:1, 50 mL). To this solution was added 1N NaOH (20 mL). Di-*tert*-butyl pyrocarbonate (5.92 g, 27.1 mmol) was added and the mixture was stirred at 20 °C. More sodium hydroxide (20 mL) was added to raise the pH to 9. After 2 h, the pH was lowered to 2.5 using 2N phosphoric acid. Dioxane was removed *in vacuo* and the aqueous solution was extracted with ethyl acetate (3 x 40 mL). The extract was dried over sodium sulfate and the solvent was removed *in vacuo* to give a clear viscous liquid (3.86 g, 98%) which was recrystallized from ethyl acetate/hexane to give 3.82 g (97%) of the N-protected serine **1a** as a white sticky solid: mp 86-88 °C (lit. mp 75-78 °C[93a], 88-89 °C[93b]); IR ($CHCl_3$ cast) 3340, 2980, 1718, 1692, 1519 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.38 (m, 2H, -O*H*, O=C-O*H*), 5.94 (m, 1H, -N*H*), 4.32 (m, 1H, -C*H*), 3.95 (m, 2H, -CH_2), 1.42 (s, 9H, -O-C(CH_3)$_3$); POSFAB MS (glycerol) 206 (MH^+).

(R)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (2a).

A modified procedure of Arnold et al.[19] was used. N-(*tert*-Butoxycarbonyl)-D-serine (**1a**) (3.56 g, 17.3 mmol) was suspended in acetonitrile/THF (9 : 1, 100 mL) in a dropping funnel placed over a 3-necked reaction flask. Triphenylphosphine (5.35 g, 20.3 mmol) was placed in the reaction flask and dissolved in acetonitrile/THF (9:1, 100 mL).

The flask was cooled to -58 °C and dimethyl azodicarboxylate (2.25 mL, 20.5 mmol) was added dropwise over 10 min. The contents of the dropping funnel were added slowly over 10 min and the mixture was stirred at -58 °C for 1 h. It was warmed to room temperature over 1 h and stirred at 20 °C for another 90 min. The solvents were removed *in vacuo* to give a light-yellow viscous liquid. This was purified by flash chromatography using ethyl acetate/hexane (35 : 65). The white powder obtained was recrystallized from ethyl acetate/carbon tetrachloride/hexane (1 : 2 : 1). The N-protected D-serine-β-lactone **2a** was obtained as white crystals (3.25 g, 64%): mp 119-120 °C (lit.[19] mp 119.5-120.5 °C); IR (CH_2Cl_2 cast) 3358, 1836, 1678, 1534 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 5.35 (m, 1H, -N*H*), 5.02 (m, 1H, -C*H*), 4.44 (d, 2H, 6 Hz, -CH_2), 1.48 (s, 9H, -C(CH_3)$_3$); exact mass 187.0840 (187.0845 calcd for $C_8H_{13}NO_4$).

(S)-N-(*tert* -Butoxycarbonyl)-α-amino-β-propiolactone (2b).

This was prepared by a procedure similar to that of the lactone **2a**. N-(*tert*-Butoxycarbonyl)-L-serine (**1b**) (4.19 g, 20.4 mmol) was reacted with triphenylphosphine (5.40 g, 20.6 mmol) and dimethyl azodicarboxylate (2.25 mL, 2.99 g, 20.5 mmol). (S)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (**2b**) was obtained as white crystals (2.34 g, 61%) with spectroscopic data identical to that of **2a** : mp 119-120 °C; $[\alpha]_D$ -26.3° (c 1, CH_3CN) (lit.[19a] $[\alpha]_D$ -26.7 (c 1, CH_3CN)).

(S)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (2b) (Prepared Using Polystyrene Resin **17**).

Methyl azodicarboxylate-polystyrene resin **17a** (9.00 g, 2.4 mequiv) was swollen briefly (15 min) in dry THF (100 mL). The stirred suspension was cooled to -45 °C and N-(*tert*-butoxycarbonyl)-L-serine (**1b**) (414 mg, 2.02 mmol) was added. To this was added dropwise a solution of triphenylphosphine (0.627 g, 2.39 mmol) in dry THF (10 mL) over 10 min. The mixture was stirred 30 min at -45 °C, allowed to warm to 0 °C over

1 h, and then stirred an additional 2 h. The temperature was raised to 25 °C and the reaction was stirred for 12 h. The mixture was filtered, and the resin was washed with dry dichloromethane (2 x 100 mL) and dry ether (100 mL). The combined filtrate and washings were concentrated *in vacuo* at 35 °C. Flash chromatography (35% ethyl acetate/hexane) of the residue yielded 187 mg (50%) of pure **2b** which possessed physical and spectral properties identical to those previously described.

2,4-Dinitro-1,5-bis-(3-hydroxypropylamino)benzene (5).

2,4-Dinitro-1,5-difluorobenzene (**4**) (0.706 g, 3.46 mmol) was dissolved in acetonitrile (20 mL) and protected from light. To this, 3-amino-1-propanol (0.55 mL, 0.540 g, 7.19 mmol) and triethylamine (0.95 mL, 0.69 g, 6.8 mmol) were added successively. The mixture was stirred at 40 °C in the dark for 24 h. The solvent was removed *in vacuo* to give 2.95 g of yellow crystals. The product was purified by flash chromatography (methanol/ethyl acetate, 1 : 9) to give 0.764 g (70%) of **5** as a yellow crystalline solid. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 131-133 °C; IR (KBr) 3363, 3347, 1625, 1584, 1536 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 9.10 (s, 1H, Ar-*H*), 8.62 (m, 2H, -N*H*), 6.09 (s, 1H, Ar-*H*), 3.98 (t, 1H, 5.2 Hz, H*H*C-OH), 3.74 (q, 3H, 5.2 Hz, H_2C-OH, H*H*C-OH), 3.56 (q, 4H, 6.4 Hz, CH_2-OH), 2.85 (m, 2H, -O*H*), 2.0 (m, 4H, -$CH_2CH_2CH_2$); ^{13}C NMR (APT, 300 MHz, acetone-d_6) δ 31.96 ($CH_2CH_2CH_2$), 41.63 (CH_2NH), 60.30 (CH_2OH), 124.69 (*Ar*-NH), 129.42 (*Ar*-H), 149.57 (*Ar*-NO_2); exact mass 314.1233 (314.1227 calcd for $C_{12}H_{18}N_4O_6$); Anal. Calcd for $C_{12}H_{18}N_4O_6$: C, 45.86; H, 5.77; N, 17.83. Found: C, 45.53; H, 5.67; N, 17.49.

2,4-Dinitro-1,5-bis-(3-acetoxypropylamino)benzene (6).

The literature[94] procedure was adopted. Compound **5** (0.187 g, 0.595 mmol) was dissolved in anhydrous pyridine (3.0 mL, 2.93 g, 37.1 mmol). Acetic anhydride (0.60

mL, 0.648 g, 6.35 mmol) was added and the mixture was stirred at 20 °C for 4 h. It was then poured onto ice (50 g), 6N HCl (20 mL), and chloroform (80 mL). The layers were separated and the organic layer was washed with 2N HCl (2 x 100 mL). The aqueous layers were combined and extracted with chloroform (2 x 50 mL). The organic layers were combined and washed with saturated sodium bicarbonate (50 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to give pure **6** as a yellow powder (0.23 g, 98%). An analytical sample was recrystallized from ethyl acetate/hexane: mp 97-98 °C; IR (KBr) 3383, 3361, 1741, 1728, 1613, 1585, 1543 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.18 (s, 1H, Ar-*H*), 8.49 (m, 2H, -N*H*), 5.64 (s, 1H, Ar-*H*), 4.26 (t, 4H, 5.8 Hz, CH_2-$OCOCH_3$), 3.40 (q, 4H, 6.6 Hz, 5.1 Hz, CH_2-NH), 2.12 (m, 10H, $-CH_2CH_2CH_2$, $O{=}C{-}CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.92 (CH_3), 27.57 ($CH_2CH_2CH_2$), 41.21 (CH_2NH), 62.50 (CH_2OH), 124.13 (*Ar*-NH), 129.49 (*Ar*-H), 148.52 (*Ar*-NO_2), 170.97 (C=O); exact mass 398.1439 (398.1439 calcd for $C_{16}H_{22}N_4O_8$); Anal. Calcd for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.34; H, 5.28; N, 13.91.

3-[N-(2,4-dinitro-5-fluorophenyl)]-aminopropyl Silica Gel (7).

3-Aminopropyl silica gel **3** (Sigma, 1.1 mmol N/g of silica, 8.7 mol% loading, 4.24 g) was suspended in dimethylformamide (60 mL) and protected from light[50b]. Triethylamine (1.80 mL, 1.31 g, 12.9 mmol) was added dropwise. A solution of 1,5-difluoro-2,4-dinitrobenzene in dimethylformamide (10 mL) was added dropwise at 20 °C. After addition was complete, the temperature was raised to 40 °C, and the mixture was stirred for 24 h. The resulting dark red suspension was filtered, and the silica gel was washed with ether (5 x 20 mL) to give 4.33 g of yellow functionalized silica gel **7**: IR (Fluorolube mull) 3362, 1634, 1624, 1584 cm^{-1}; Anal. Calcd (av unit formula $C_{0.783}H_{1.696}N_{0.261}Si_{1.261}O_{2.696}F_{0.087}$, av formula weight 98.81/unit, 0.92 mequiv/g for maximum theoretical 8.7 mol% loading) C, 9.91; H, 1.80; N, 3.85. Found: C, 9.57; H, 1.13; N, 3.38.

For 3-aminopropyl silica gel **3**: IR (Fluorolube mull) 3600-3000, 2940, 1565 cm^{-1}; Anal. Calcd (av unit formula $C_{0.2598}H_{1.6062}N_{0.0866}Si_{1.2598}O_{2.3464}$, av formula weight 78.72/unit, 1.1 mequiv/g, 8.7 mol% loading) C, 3.96; H, 2.06; N, 1.54. Found: C, 5.85; H, 1.32; N, 2.00.

1,2-Bis-(N'-methoxycarbonyl-N-azocarbonyloxymethyl)benzene (8).

Literature procedure[51] was adopted to oxidize **10** with N-bromosuccinimide. The hydrazodicarboxylate **10** (94.8 mg, 0.256 mmol) was dissolved in dichloromethane (30 mL) and pyridine (0.02 mL, 20.6 mg, 0.260 mmol) was added dropwise at 25 °C. N-Bromosuccinimide (45.2 mg, 0.254 mmol) was added in portions over 20 min and then the mixture was stirred for 1 h. The resulting yellow solution obtained was washed successively with water (2 x 20 mL), 10% sodium hydroxide (20 mL) and water (2 x 20 mL). The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo* to give the azodicarboxylate **8** as a yellow oil (81.0 mg, 85%): IR ($CHCl_3$ cast) 1746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48 (m, 4H, Ar-*H*), 5.60 (s, 4H,-C*H*$_2$), 4.08 (s, 6H,-C*H*$_3$); CI MS (NH_3) 384 (MNH_4^+).

1,2-Bis-(N'-methoxycarbonyl-N-hydrazocarbonyloxymethyl)benzene (10) (Prepared from **11**).

Compound **11** (13.0 g, 34.4 mmol) was dissolved in dimethylformamide (250 mL). Methyl carbazate (18.6 g, 206 mmol) and 4-(dimethylamino)pyridine (12.6 g, 103 mmol) were added. The reaction was stirred at 25 °C for 15 days. Dimethylformamide was distilled off (35 °C at 3 mm Hg) to give a dark yellow oil. This was purified by flash chromatography (ethyl acetate/chloroform (4 : 1)) and MPLC RP-8 (acetonitrile/water 3 : 7, 3 mL/min, 3 min fractions) successively to give the pure **10** as a white solid (9.03 g, 71%): mp 162-164 °C; IR (KBr) 3300, 1720, 1526 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$-DMSO-d_6 (5 : 1)) δ 8.22 (m, 4H, -N*H*), 7.36 (m, 4H, Ar-*H*), 5.19 (s, 4H, -C*H*$_2$), 3.68

(s, 6H, -C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$-DMSO-d_6 (5 : 1)) δ 36.6 (*C*H_3), 50.85 (*C*H_2), 127.21 (*Ar*), 128.75 (*Ar*), 133.67 (*Ar*), 155.25 (*C*=O), 156.20 (*C*=O); exact mass 370.1115 (370.1125 calcd for $C_{14}H_{18}N_4O_8$); CI MS (NH_3) 388 (MNH_4^+); Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.90; N, 15.13. Found C, 45.27; H, 4.97; N,14.88.

1,2-Bis-(N'-methoxycarbonyl-N-hydrazocarbonyloxymethyl)benzene (10) (Prepared from **9**).

A sample of 1,2-benzenedimethanol (**9**) (1.19 g, 8.59 mmol) was dissolved in THF (90 mL), and phosgene (2.40 mL, 3.48 g, 35.2 mmol) was bubbled into the solution in the hood. Triethylamine (2.4 mL, 1.74 g, 17.2 mmol) was added and the mixture was stirred at 25 °C for 24 h. This was filtered under argon to remove triethylamine hydrochloride salt, and a suspension of methyl carbazate (1.61 g, 17.8 mmol) in THF (20 mL) was added. Triethylamine (2.40 mL, 1.74 g, 17.2 mmol) was added, and the mixture was stirred at 25 °C for 6 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate/chloroform 4 : 1) to give the hydrazodicarboxylate **10** (1.52 g, 69 %), which possessed spectral and chromatographic properties identical to **10** obtained from **11**.

1,2-Bis-[(phenoxycarbonyl)oxymethyl]benzene (11).

A sample of 1,2-benzenedimethanol (**9**) (5.04 g, 36.5 mmol) was dissolved in dry dichloromethane (80 mL) and cooled to 0 °C. Phenyl chloroformate (13.6 mL, 17.0 g, 108 mmol) and pyridine (5.90 mL, 5.77 g, 72.9 mmol) were added. Evolution of gas was observed and the solution became clear and colourless. When addition was complete, the solution became light yellow in colour, and a thick white precipitate was formed. The mixture was stirred at 0 °C for 6 h and warmed slowly to 25 °C overnight. The mixture was filtered and the solvent was removed *in vacuo*. Pure **11** was obtained as a white solid

(13.8 g, 99%): mp 44-45 °C; IR (KBr) 1761, 1752, 1494 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 14H, Ar-*H*), 5.42 (s, 4H, -CH_2); CI MS (NH_3) 396 (MNH_4^+); Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.84; H, 4.79. Found: C, 69.57; H, 4.93.

Hydroxymethyl Polystyrene Resin (12b).

Acetoxymethyl polystyrene resin **14** (31.2 g, 3.57 mequiv/g, 111 mequiv) was suspended in dimethylformamide (450 mL) and anhydrous hydrazine (100 g, 3.13 mol) was added. The mixture was stirred under argon at 20 °C for 24 h. The resin was filtered, and washed successively with acetonitrile (2 x 400 mL), methanol (400 mL) and ether (2 x 400 mL). The material was dried *in vacuo* at 35 °C to give hydroxymethyl polystyrene **12**: IR (Fluorolube mull) 3360, 3060, 3020, 2920, 2860, 1601 cm^{-1}. Anal. Calcd (av unit formula $C_{8.501}H_{9.002}O_{0.501}$, av formula weight 119.19/unit, 50.1 mol% loading, 4.20 mequiv/g): C, 85.66; H, 7.61. Found: C, 85.72; H, 7.73.

Acetoxymethyl Polystyrene Resin (14).

The procedure of Wang[53] was employed. Chloromethyl polystyrene resin (Biobeads S-X1, 3.90 mequiv/g, 30.0 g, 117 mequiv) was suspended in dimethylacetamide (700 mL) and stirred gently with potassium acetate (17.2 g, 176 mmol) at 80 °C for 28 h. The hot suspension was filtered, washed successively with water/dimethylformamide (1 : 1, 2 x 500 mL), dioxane (3 x 250 mL), methanol (2 x 300 mL), and ether (2 x 300 mL). The resulting white resin was dried *in vacuo* at 50 °C to give acetoxymethyl polystyrene **14**: IR (Fluorolube mull) 3010, 2920, 1736, 1601 cm^{-1}. Anal. Calcd (av unit formula $C_{9.503}H_{10.004}O_{1.002}$, av formula weight 140.25/unit, 3.57 mequiv/g based on maximum theoretical 50.1 mol% loading): C, 81.38; H, 7.19. Found: C, 81.05; H, 7.09.

Methyl Hydrazodicarboxylate Polystyrene Resin (15b) (Prepared from **11b**).

The polystyrene **11b**, obtained from treatment of hydroxymethyl polystyrene resin **12b** with phenyl chloroformate, was immediately resuspended in dimethylformamide (450 mL) and water (25 mL). Methyl carbazate (30.0 g, 333 mmol) and 4-(dimethylamino)pyridine (20.4 g, 167 mmol) were added and the mixture was stirred slowly at 20 °C under argon for 5 days. The resin was filtered and washed successively with methanol/water (1 : 1, 3 x 400 mL), methanol (450 mL), THF (450 mL), and ether (3 x 450 mL). The snowy-white polystyrene resin **15b** was dried *in vacuo* at 60 °C: IR (Fluorolube mull) 3300, 3060, 3020, 2980, 2940, 2860, 1740 cm^{-1}. Anal. Calcd (av unit formula $C_{10.004}H_{11.006}N_{1.002}O_{2.004}$, av formula weight 177.35/unit, based on maximum theoretical 50.1 mol% loading, 2.83 mequiv/g): C, 67.75; H, 6.26; N, 7.91. Found: C, 73.30; H, 6.26; N, 4.85.

Methyl Hydrazodicarboxylate Polystyrene Resin (15b) (Prepared from **12b**).

Hydroxymethyl polystyrene resin **12b** (3.23 g, 4.20 mequiv/g) was suspended in dry THF (100 mL) in the hood. Phosgene (5.20 mL, 7.48 g, 75.6 mmol) and pyridine (1.00 mL, 0.978 g, 12.6 mmol) were added successively and the mixture was stirred for 2 h at 20 °C. The resin was filtered and washed with dry dichloromethane (5 x 75 mL). All filtrates were treated with aqueous ammonia in the hood to destroy the toxic phosgene. The resin was resuspended in dichloromethane (100 mL) and methyl carbazate (3.40 g, 37.8 mmol) was added. Triethylamine (1.7 mL, 1.28 g, 12.6 mmol) was added dropwise, and the mixture was stirred at 20 °C for 2 h. The resin was filtered and washed successively with methanol/water (1:1, 2 x 50 mL), methanol (50 mL), dichloromethane (2 x 50 mL) and ether (3 x 100 mL). The resin was dried *in vacuo* at 20 °C to give white methyl hydrazodicarboxylate-polystyrene resin **15b**: IR (Fluorolube mull) 3300, 3060, 3020, 2980, 2940, 2860, 1740cm^{-1}; Anal. Calcd (av unit formula $C_{10.004}H_{11.006}N_{1.002}O_{2.004}$,

av formula weight 177.35/unit based on maximum theoretical 50.1 mol % loading, 2.83 mequiv/g): C, 67.75; H, 6.26; N, 7.91. Found: C, 68.48; H, 6.50; N, 6.72.

Methyl Hydrazodicarboxylate Polystyrene Resin (15a) (Prepared from **12a**).

Hydroxymethyl polystyrene resin **12a** (1% crosslinked with divinyl benzene, 0.55 mequiv/g, 5.8 mol% loading, 10.0 g) was suspended in dichloromethane (250 mL) in the hood. Excess phosgene was bubbled into the suspension at 20 °C. Pyridine (0.44 mL, 0.430 g, 5.44 mmol) was added and the mixture was stirred for 1.5 h. The polystyrene resin was filtered and washed with dry dichloromethane (2 x 75 mL). All filtrates were treated with aqueous ammonia before they were discarded. The resin was directly resuspended in dry dichloromethane (250 mL) and methyl carbazate (1.50 g, 16.7 mmol) and 4-(dimethylamino)pyridine (1.01 g, 8.27 mmol) were added. The mixture was stirred at 20 °C for 20 h. The resin was filtered and washed successively with methanol/water (1 : 1, 200 mL), methanol (200 mL), dichloromethane (200 mL) and ether (3 x 200 mL). The resin was dried *in vacuo* at 20 °C to give white methyl hydrazodicarboxylate-polystyrene resin **15a**: IR (Fluorolube mull) 3300, 3060, 3020, 2980, 2940, 2860, 1740 cm^{-1}. Anal. Calcd (av unit formula $C_{8.232}H_{8.348}N_{0.116}O_{0.232}$, av formula weight 112.63/unit, based on maximum theoretical 5.8 mol% loading, 0.52 mequiv/g): C, 87.79; H, 7.47; N, 1.44. Found: C, 87.56; H, 7.50; N, 1.10.

Reaction of Methyl Hydrazodicarboxylate Polystyrene Resin (15b) with Chlorine Gas.

Chlorine gas (4.5 mL, 7.04 g, 99.3 mmol) was bubbled quickly into a suspension of the hydrazodicarboxylate polystyrene resin **15b** (8.00 g, 17.0 mequiv) in dry dichloromethane (200 mL) at 25 °C. The reaction mixture was stirred in the dark for 6 h. After filtration, the resin was washed with water (2 x 200 mL) and ether (2 x 200 mL). The yellow resin **17b** was dried at 30 °C *in vacuo*: IR (Fluorolube mull) 3300, 3080, 3060,

3020, 2920, 2845, 1780, 1600 cm^{-1}. Anal. Calcd (av unit formula $C_{10.004}H_{10.004}N_{1.002}O_{2.004}$, av unit formula weight 176.34/unit based on maximum theoretical 50.1 mol% loading, 2.84 mequiv/g): C, 68.14; H, 5.72; N, 7.96; Cl, 0.0. Found: C, 61.84; H, 5.09; N, 4.55; Cl, 16.63.

(Phenoxycarbonyl)oxymethyl Polystyrene Resin (16b) (Prepared from **12b**).

The hydroxymethyl resin **12b** (26.4 g, 4.20 mequiv/g, 111 mequiv) was suspended in dichloromethane (430 mL) and cooled to 0 °C. Phenyl chloroformate (208 mL, 26.0 g, 166 mmol) was added. Pyridine (14.5 mL, 14.3 g, 181 mmol) was added carefully dropwise, and the mixture was stirred slowly at 0 °C for 6 h. The mixture was allowed to warm to 25 °C and was stirred for 15 h. The resin was filtered and washed successively with dichloromethane (2 x 400 mL), acetone (2 x 400 mL), THF (400 mL), and dry ether (2 x 400 mL). The resulting polystyrene **16b** was removed and dried *in vacuo* for analysis: IR (Fluorolube mull) 3060, 3030, 2931, 2840, 1754 cm^{-1}. Anal. Calcd (av unit formula $C_{12.008}H_{11.006}O_{1.503}$, av formula weight 254.28/unit, 50.1 mol% loading, 2.78 mequiv/g): C, 80.41; H, 6.18. Found: C, 80.05; H, 5.98.

(Phenoxycarbonyl)oxymethyl Polystyrene Resin (16a) (Prepared from Commercial Hydroxymethyl Polystyrene **12a**).

Hydroxymethyl polystyrene resin **12a** (1% crosslinked with divinyl benzene, 0.55 mequiv/g, 5.8 mol% loading, 20.0 g) was treated with phenyl chloroformate (2.07 mL, 2.58 g, 16.5 mmol) and pyridine (0.90 mL, 0.880 g, 11.1 mmol) using a procedure similar to that described for preparation of **16b**: IR (Fluorolube mull) 3080, 3060, 3020, 2920, 2850, 1760, 1715, 1600 cm^{-1}. Anal. Calcd (av unit formula $C_{8.464}H_{8.348}O_{0.174}$, av formula weight 112.86/unit, 5.8 mol% loading, 0.51 mequiv/g): C, 90.08; H, 7.46. Found: C, 90.02; H, 7.57.

Methyl Azodicarboxylate Polystyrene Resin (17b) (Prepared By Oxidation of **15b** with N-Bromosuccinimide).

Methyl hydrazodicarboxylate polystyrene (3.06 g, 8.6 mequiv) in dichloromethane (90 mL) was treated with pyridine (0.70 mL, 8.7 mmol). The mixture was protected from light and N-bromosuccinimide (1.70 g, 9.6 mmol) was added in small portions over 10 min with stirring. The mixture was stirred 1 h at 20 °C, filtered, and washed successively with acetonitrile (5 x 50 mL) and ether (2 x 500 mL). The yellow-orange resin **17b** was dried at 30 °C *in vacuo*: IR (Fluorolube mull) 3060, 3020, 2920, 2845, 1780, 1600 cm^{-1}; Anal. Calcd (av unit formula $C_{10.004}H_{10.004}N_{1.002}O_{2.004}$, av formula weight 176.34/unit based on maximum theoretical 50.1 mol % loading, 2.84 mequiv/g): C, 68.14; H, 5.72; N, 7.96. Found: C, 69.11; H, 6.01; N, 6.76.

Methyl Azodicarboxylate Polystyrene Resin (17a) (Prepared By Oxidation of **15a** with N-Bromosuccinimide).

The procedure used for preparation of **17b** was adopted. The methyl hydrazodicarboxylate polystyrene **15a** (9.00 g, 3.58 mequiv based on N analysis) was allowed to react with N-bromosuccinimide (0.937 g, 5.26 mmol) and pyridine (0.28 mL, 0.278 g, 3.51 mmol): IR (Fluorolube mull) identical to that of **17b**. Anal. Calcd (av unit formula $C_{8.232}H_{8.232}N_{0.116}O_{0.232}$, av formula weight 112.51/unit based on maximum theoretical 5.8 mol% loading, 0.52 mequiv/g): C, 87.88; H, 7.38; N, 1.44. Found: C, 86.52; H, 7.38; N, 0.96.

Methyl Azodicarboxylate Polystyrene Resin (17a) (Prepared By Oxidation of **15a** with Chlorine/Water).

The polystyrene **15a** (2.02 g, 0.81 mequiv) in THF/H_2O (1/1 (v/v), 40 mL) was cooled to 4 °C, protected from light, and treated with chlorine gas (ca. 1.1 equiv). The mixture was stirred at 5-10 °C for 6 h, and then filtered. The resin was washed with water

(2 x 200 mL), 10% sodium bicarbonate (2 x 200 mL), water (2 x 200 mL), acetone (200 mL), and ether (2 x 200 mL). It was dried at 40 °C *in vacuo* to give **17a**: IR (Fluorolube mull) 3060, 3020, 2920, 2845, 1780, 1600 cm^{-1}. Anal. Calcd (av unit formula $C_{8.232}H_{8.232}N_{0.116}O_{0.232}$, av formula weight 112.15/unit based on maximum theoretical 5.8 mol % loading, 0.52 mequiv/g): C, 87.88; H, 7.38; N, 1.44. Found: C, 86.41; H, 7.44; N, 1.11.

Methyl Azodicarboxylate Polystyrene Resin (17a) (Prepared By Oxidation of **15a** with Nitrogen Tetroxide Gas).

The hydrazodicarboxylate resin **15a** (2.06 g, 0.82 mequiv) was suspended in dichloromethane (150 mL) and cooled to 0 °C. Nitrogen tetroxide gas was bubbled through the solution for ~1 min. The temperature was raised to 20 °C and argon was bubbled through the solution to expel excess reagent.The resulting yellow resin was filtered and washed with dichloromethane (2 x 150 mL) and ether (2 x 150 mL) to give the azodicarboxylate resin **17a**: IR (Fluorolube mull) 3080, 3060, 3020, 2920, 2845, 1780, 1600 cm^{-1}; Anal. Calcd (av unit formula $C_{8.232}H_{8.232}N_{0.116}O_{0.232}$, av. unit formula weight 112.51/unit based on maximum theoretical 5.8 mol% loading, 0.52 mequiv/g): C, 87.88; H, 7.38; N, 1.44. Found: C, 87.02; H, 7.67; N, 1.54.

Determination of Available Reactive Sites on Methyl Azodicarboxylate-Polystyrene Resins 17.

In a typical procedure, resin **17a** (0.111 g, 0.043 mequiv based on N analysis) was suspended in THF (10 mL) and a solution of excess triphenylphosphine (60.5 mg, 0.231 mmol) in THF (5 mL) was added at 25 °C. The mixture was stirred 30 min and quenched with excess water (ca. 1 mL). The resin was filtered and washed with THF and methanol. The combined filtrate and washings were concentrated to dryness *in vacuo* and redissolved in CD_3OD or acetone-d_6. Integration of the peaks at 7.5 δ (Ph_3PO) and 7.3 δ (Ph_3P) in the

^1H NMR spectrum provided the proportion of triphenylphosphine which was converted (after correction for any residual Ph_3PO in the Ph_3P starting material).

Test of Triphenylphosphine/Water Reaction on a Non-Oxidized Polystyrene.

The hydrazodicarboxylate polystyrene **15a** (95.6 mg) was suspended in THF (5 mL) with triphenylphosphine (0.124 g, 0.472 mmol) and triphenylphosphine oxide (0.118 g, 0.424 mmol) (i.e., total weight of Ph_3P and Ph_3PO = 0.242 g, ratio of Ph_3P : Ph_3PO = 1 : 0.95 after consideration of 2.7% residual Ph_3PO in the Ph_3P used). The mixture was stirred for 30 min and quenched with water (0.2 mL). After an additional 15 min, the mixture was filtered and washed with acetone (4 x 10 mL). The solvent was removed *in vacuo* and the residue from the filtrate was dried (wt recovered = 0.241 g). The residue was dissolved in acetone-d_6. The ^1H NMR spectrum showed ratio of Ph_3P : Ph_3PO recovered = 1 : 0.96. The recovered polystyrene was dried under vacuum (wt recovered = 81.7 mg). Anal. Calcd (av unit formula $C_{8.232}H_{8.348}N_{0.116}O_{0.232}$, av formula weight 112.63/unit, based on maximum theoretical 5.8 mol% loading, 0.52 mequiv/g): C, 87.79; H, 7.47; N, 1.44. Found (for resin in its initial state): C, 87.85; H, 7.63; N, 1.53. Found (for recovered resin): C, 87.38; H, 7.66; N, 1.38.

(2R)-2-[N-(*tert*-Butoxycarbonyl)amino]-3-[(2R)-2-carboxy-2-N-(*tert*-butoxycarbonyl)amino)ethylamino]propionic Acid (18).

Potassium hydride (21.7 mg of hydride in 35% suspension in oil, 0.541 mmol) was weighed in a dry reaction flask under argon. The hydride was washed with dry THF (2 x 2 mL) under argon and resuspended in THF (2 mL). (R)-N-*tert*-Butoxycarbonyl-D-2,3-diaminopropionic acid (**21a**) (0.111 g, 0.544 mmol) was dissolved in THF (2 mL) and added to the THF suspension of potassium hydride. The mixture was stirred for 20 min at 25 °C. (R)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (**2a**) (0.102 g, 0.545

mmol) was dissolved in THF (3 mL) and added dropwise to the mixture over 10 min. This was then cooled to 0 °C and stirred for 4 h. The solvent was removed *in vacuo* and the residue was dissolved in water and acidified to pH 4 using dilute acetic acid. The solution was concentrated *in vacuo* and purified by reverse phase medium pressure liquid chromatography (MPLC) (RP-8, CH_3CN : H_2O 6 : 4, 3 mL/min, 3 min fractions). The product **18** was obtained as an oil (6.0 mg, 3%): ^1H NMR (300 MHz, D_2O, TSP) δ 4.07 (t, 2H, 5 Hz, -C*H*), 3.83 (d, 4H, 3.5 Hz, -CH_2), 1.43 (s, 18H, -C(CH_3)$_3$); EI MS 277 [M - (2 x 57 ((CH$_3$)$_3$C+))]. Compound **18** was deprotected by heating with trifluoroacetic acid (5 min) to give **18a** (5.7 mg, 95%): IR (KBr) 3524-3349, 3220, 1740, 1630, 1405; POSFAB MS (glycerol/HCl) 193 (MH_2^+).

(2S)-2-(N-Benzyloxycarbonyl)-3-[(2S)-2-carboxy-2-(N-(*tert*-butoxycarbonyl)amino)ethylamino]propionic Acid (19).

Potassium hydride (89.6 mg of hydride in 35% suspension in oil, 2.23 mmol) was weighed under argon. It was washed with THF (2 x 2 mL) and suspended in THF (2 mL). (S)-N-(Benzyloxycarbonyl)-L-2,3-diaminopropionic acid (Fluka) (0.537 g, 2.25 mmol) was suspended in THF (30 mL) and added to the potassium hydride. The mixture was stirred for 15 min. A solution of 18-crown-6 (0.576 g, 2.18 mmol) in THF (2 mL) was added to the mixture of hydride and amine. The resulting mixture was stirred for 1 h. (S)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (**2b**) (0.263 g, 1.41 mmol) was dissolved in THF (2 mL) and added dropwise. The mixture was stirred at 25 °C for 14 h. The solvent was removed *in vacuo*, and the residue was dissolved in water and acidified to pH 4 using dilute acetic acid. The solution was concentrated *in vacuo* and purified by MPLC (RP-8, CH_3CN : H_2O 1 : 1, 3 mL/min, 3 min fractions) followed by preparative TLC (methanol/ethyl acetate (3 : 2)). The product **19** was obtained as an oil (5.4 mg, 1%): IR ($CHCl_3$ cast) 3300, 2950, 1717, 1600, 1529, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, Ar-*H*), 5.88 (m, 1H, -C*H*), 5.10 (s, 2H, CH_2-Ar), 4.42, (m, 1H, -C*H*),

3.13 (m, 2H, -CH_2), 1.35 (s, 9H, -C(CH_3)$_3$); POSFAB MS (glycerol/HCl) 426 (MH^+), 370 [MH^+ - 57 ($(CH_3)_3C^+$)], 280 [MH_2^+ - ($(CH_3)_3C^+$, $PhCH_2$)].

N'-(Propyl)-N-(*tert*-butoxycarbonyl)-L-2,3-diaminopropionic Acid (20).

(S)-N-(*tert*-Butoxycarbonyl)-α-amino-β-propiolactone (**2b**) (61.4 mg, 0.33 mmol) was dissolved in THF (5.0 mL) and cooled to 0 °C. n-Propylamine (0.14 mL, 100 mg, 1.70 mmol) was added and the mixture was stirred at 0 °C for 2 h. THF was removed *in vacuo* and the product was recrystallized from methanol/ether to give pure **20** (78.9 mg, 98%): IR (MeOH cast) 3313, 2969, 2934, 1700, 1654, 1528 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 7.70 (m, 1H, -N*H*), 6.50 (m, 1H, -N*H*), 3.95 (m, 1H, *H*CNH), 3.56 (m, 2H, CH_2CH), 3.04 (q, 2H, 7 Hz, NCH_2CH_2), 2.52 (m, 2H, CH_2CH_3), 0.85 (t, 3H, 7Hz, -CH_3); POSFAB MS (glycerol/HCl) 247 (MH^+).

N-(*tert*-Butoxycarbonyl)-D-2,3-diaminopropionic Acid (21a).

The general procedure of Arnold et al.[19] was adopted. (R)-N-*tert*-Butoxycarbonyl-α-amino-β-propiolactone (**2a**) (0.374 g, 2.00 mmol) was dissolved in THF (28 mL) and cooled to 0 °C. Ammonia gas was bubbled into the solution for 1h. The reaction mixture was stirred for another 2h. The solvent was removed *in vacuo* and the residue was dissolved in water (20 mL) and extracted with ether (4 x 30 mL). The aqueous layer was concentrated *in vacuo* and dried under vacuum over calcium sulfate to give 0.323 g (79%) of white solid. Recrystallization from methanol/ether gave the N-protected D-diaminopropionic acid **21a** as a white solid (0.301 g, 74%): mp 197-198 °C (lit.[67] mp 198-200 °C); IR ($CHCl_3$ cast) 3320, 2980, 1674, 1515 cm^{-1}; ^1H NMR (80 MHz, D_2O, TSP) δ 4.15 (t, 1H, -C*H*), 3.81 (d, 2H, -CH_2), 1.42 (s, 9H, -C(CH_3)$_3$); POSFAB MS (glycerol) 205 (MH^+), 149 (MH_2^+ - 57 ($(CH_3)_3C^+$), 100%).

N-(*tert*-Butoxycarbonyl)-L-2,3-diaminopropionic Acid (21b).

The monoprotected L-2,3-diamino propionic acid **21b** was prepared using a procedure similar to that for **21a**. (S)-N-*tert*-Butoxycarbonyl-α-amino-β-propiolactone (**2b**) (0.291 g, 1.56 mmol) in THF (12 mL) was reacted with ammonia gas at 0 °C. Work-up and recrystallization from methanol/ether gave 0.258 g (81%) of **21b** as a white solid: mp 197-199 °C; Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 46.83; H, 7.78; N, 13.86.

N-(*tert*-Butoxycarbonyl)-L-2,3-diaminopropionic acid (21b) (Prepared from **22**).

The procedure of Waki et al.[67] was adopted. N-(*tert*-Butoxycarbonyl)-L-asparagine (**22**) (2.32 g, 9.99 mmol) was added to a solution of [bis(trifluoroacetoxy)iodo]benzene (6.45 g, 15.0 mmol) in dimethylformamide/water (1:1 (v/v), 80 mL). The mixture was stirred for 15 min at 25 °C. Pyridine (1.6 mL, 1.56 g, 19.8 mmol) was added and the mixture was stirred for 3 h. The clear yellow solution obtained was concentrated *in vacuo*, and the residue was dissolved in water (70 mL). The aqueous solution was washed with ether (3 x 50 mL) and the water was removed *in vacuo*. A white residue was obtained which was recrystallized from methanol/ether to give N-(*tert*-butoxycarbonyl)-L-2,3-diaminopropionic acid **21b** (1.78 g, 87%) with spectral and chromatographic properties identical to those of **21b** prepared from **2b**.

N-(*tert*-Butoxycarbonyl)-L-asparagine (22).

L-Asparagine (0.944 g, 7.15 mmol) and di-*tert*-butyl pyrocarbonate (1.56 g, 7.14 mmol) were stirred in dioxane/water (2:1, 30 mL) at 25 °C. Sodium hydroxide (1N, 15 mL) was added to keep the pH at ~9. After 2.5 h, pH was lowered to 2 using 2N H_3PO_4. The product was isolated as described for **1a** to give 1.07 g (65%) of N-(*tert*-butoxycarbonyl)-L-asparagine (**22**) as a white solid. An analytical sample was

recrystallized from methanol/ethyl acetate/hexane (2 : 1 : 1): mp 178-179 °C (lit.[95] mp 181-182 °C); IR (KBr) 3416, 2960, 1741, 1722, 1689, 1662, 1589, 1531 cm^{-1}; ^1H NMR (80 MHz, CD_3OD) δ 4.42 (t, 1H, 6 Hz, -C*H*), 2.75 (d, 2H, 6 Hz, -CH_2), 1.45 (s, 9H, -O-C(CH_3)$_3$); CI MS (NH_3) 233 (MH^+), 250 (MNH_4^+).

L-2,3-Diaminopropionic Acid (23).

A sample of N-(*tert*-butoxycarbonyl)-L-2,3-diaminopropionic acid (**21b**) was deprotected by heating with concentrated hydrochloric acid for 3 min. Drying of the mixture under vacuum gave **23**: IR (KBr) 3000-3200, 2933, 1618, 1552, 1480 cm^{-1}; ^1H NMR (80 MHz, D_2O, TSP) δ 4.07 (t, 1H, 7.5 Hz, -C*H*), 3.50 (d, 2H, 7.5 Hz, -CH_2); POSFAB MS (glycerol/HCl) 105 (MH^+, 100%).

Benzyl Benzoate (25) (Prepared Using Dimethyl Azodicarboxylate).

Triphenylphosphine (0.785 g, 3.00 mmol) and benzyl alcohol (0.360 mL, 0.378 g, 3.50 mmol) were dissolved in THF (2mL). This solution was added dropwise to a solution of dimethyl azodicarboxylate. (0.33 mL, 0.438 g, 3.00 mmol) and benzoic acid (0.367 g, 3.01 mmol) in THF (3 mL). The mixture was stirred at 25 °C for 20 h. The solvent was removed and the resulting yellow oily compound was purified by flash chromatography (3.5% ethyl acetate in hexane) to give 0.524 g (82%) of benzyl benzoate **25**:[69a] IR (film) 1720, 1600, 1272 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.0 (m, 2H, Ar-*H*), 7.20 (m, 8H, Ar-*H*), 5.25 (s, 2H, -CH_2); exact mass 212.0839 (212.0838 calcd for $C_{14}H_{12}O_2$).

Benzyl Benzoate (25) (Prepared Using Polystyrene Resin **17b**).

Resin **17b** (8.00 g, 2.21 mequiv) was swollen in dry THF (100 mL) for 15 min. A solution of triphenylphosphine (0.576 g, 2.20 mmol), benzoic acid (0.234 g, 1.92 mmol) and benzyl alcohol (0.20 mL, 0.209 g, 1.93 mmol) in THF (5 mL) was added dropwise. The resin was stirred at 25 °C for 20 h then filtered, and washed with dichloromethane (4 x

150 mL). The combined filtrate and washings were concentrated *in vacuo* at 30 °C, and purified by flash chromatography (3.5% ethyl acetate/hexane) to yield 0.251 g (61%) of benzyl benzoate (**25**) with physical and spectral properties identical to those previously described.

n-Propyl Benzoate (26) (Prepared Using Dimethyl Azodicarboxylate).

Benzoic acid (1.22 g, 10.0 mmol) was dissolved in anhydrous ether (10 mL). Dimethyl azodicarboxylate (1.10 mL, 1.46 g, 10.0 mmol) was added dropwise to the reaction flask at 25 °C. Triphenylphosphine (2.62 g, 10.0 mmol) and n-propanol (1.12 mL, 0.901 g, 15.0 mmol) were dissolved in ether (10 mL) and added dropwise. A precipitate appeared during addition but disappeared after addition was complete. The clear yellow solution was stirred at 25 °C for 20 h. The solvent was removed *in vacuo* and purified by flash chromatography (0.5% ethyl acetate in hexane) to give 0.912 g (56%) of n-propyl benzoate (**26**)[69b] as a yellowish liquid: IR (film) 2970, 1721, 1600, 1276 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.30 (m, 2 H, Ar-*H*), 7.43 (m, 3 H, Ar-*H*), 4.25 (t, 2 H, 7 Hz, $-OCH_2$), 1.75 (m, 2 H, $-CH_2CH_3$), 0.98 (t, 3 H, 7 Hz, $-CH_2CH_3$); exact mass 164.0836 (164.0838 calcd for $C_{10}H_{12}O_2$).

n-Propyl Benzoate (26) (Prepared Using Polystyrene Resin **17a**).

The procedure used to make **25** was employed to convert benzoic acid (0.134 g, 1.10 mmol) and n-propanol (0.180 g, 3.00 mmol) with resin **17a** (4.0 g, 1.1 mequiv) and triphenylphosphine (0.288 g, 1.11 mmol) to n-propyl benzoate (**26**) in 55% yield after flash chromatography (0.5% ethyl acetate/hexane) with physical and spectral properties identical to those previously described.

Ethyl 2-Cyanopentanoate (28).

Resin **17a** (0.502 g, 0.90 mequiv) was suspended in dry THF (30 mL) and a solution of triphenylphosphine (0.235 g, 0.896 mmol) in THF (5 mL) was added. The mixture was then treated dropwise with a solution of ethyl cyanoacetate (32.0 mg, 0.281 mmol) and n-propyl alcohol (16.0 mg, 0.267 mmol) in THF (2 mL). The mixture was stirred at 20 °C for 24 h. The resin was filtered and washed with THF (2 x 5 mL). The combined filtrate and washings were concentrated *in vacuo* and the resulting residue was purified by flash chromatography (ethyl acetate/hexane, 3:2) to give ethyl 2-cyanopentanoate (**28**) as an oil (18 mg, 42%)[41]: IR ($CHCl_3$ cast) 2966, 2939, 2878, 2241, 1746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.27 (q, 2 H, 7 Hz, -OC*H*$_2$), 3.52 (t, 1 H, 7 Hz, C*H*), 1.94 (m, 2 H, C*H*$_2$CH), 1.56 (m, 2 H, CH_3C*H*$_2$), 1.34 (t, 3 H, 7.5 Hz, C*H*$_3$$CH_2O$), 1.02 (t, 3 H, 7 Hz, C*H*$_3$$CH_2$); exact mass 155.0947 (155.0946 calcd for $C_8H_{13}NO_2$).

N-Benzylphthalimide (29).

The polystyrene reagent **17a** (4.0 g, 1.12 mequiv) was suspended in dry THF (150 mL) for 15 min. A solution of triphenylphosphine (0.295 g, 1.13 mmol), phthalimide (0.170 g, 1.16 mmol), and benzyl alcohol (0.119 g, 1.10 mmol) in THF was added dropwise and the mixture was stirred at 25 °C for 23 h. The resin was filtered and washed with THF (2 x 100 mL) and with ether (2 x 100 mL). The combined filtrate and washings were concentrated *in vacuo* and the residue was purified by flash chromatography (ethyl acetate/hexane, 1:3) to give 0.149 g (57%) of N-benzylphthalimide (**29**)[42]: mp 109-110 °C (lit.[96] mp 114-115 °C); IR (KBr) 1773, 1702, 1612 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (m, 2 H, Ar-*H*), 7.73 (m, 2 H, Ar-*H*), 7.46 (m, 2 H, Ar-*H*), 7.33 (m, 3 H, Ar-*H*), 4.88 (s, 2 H, -C*H*$_2$); exact mass 237.0791 (237.0790 calcd for $C_{15}H_{11}NO_2$); Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.83; H, 4.65; N, 5.71.

N-(Phthaloyl)-D-alanine Ethyl Ester (30) (Prepared Using Polystyrene Resin **17b**).

Resin **17b** (1.78 g, 3.8 mequiv) was suspended in dry THF (130 mL). A solution of phthalimide (0.432 g, 2.94 mmol), triphenylphosphine (1.03 g, 3.93 mmol), and (S)-(-)-ethyl-lactate (**31**) (0.340 g, 2.88 mmol) ($[\alpha]_D$ -11.5 (neat)) in THF (10 mL) was added dropwise, and the mixture was stirred at 20 °C for 48 h. The resin was filtered and washed successively with methanol (2 x 75 mL), chloroform (2 x 75 mL), and ether (3 x 100 mL). The combined filtrate and washings were concentrated *in vacuo*. The residue was separated by flash chromatography (ethyl acetate/hexane, 1/3) and then recrystallized from ether to give **30** (0.322 g, 45%): mp 57-58 °C (lit.[42] mp 60-61 °C); $[\alpha]_D$ +18.2 (c 1, MeOH), $[\alpha]_D$ +4.9 (c 1, $CHCl_3$); IR (KBr) 1736, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2 H, Ar*H*), 7.75 (m, 2 H, Ar*H*), 4.95 (q, 1 H, 7.4 Hz, C*H*CH_3), 4.22 (q, 2 H, 7.0 Hz, OCH_2), 1.70 (d, 3 H, 7.4 Hz, CHCH_3), 1.22 (t, 3 H, 7 Hz, CH_2CH_3); exact mass 247.0846 (247.0845 calcd for $C_{13}H_{13}NO_4$); Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.18; H, 5.06; N, 5.67.

N-(Phthaloyl)-D-alanine Ethyl Ester (30) (Prepared By Esterification of **33**).

The literature[42] procedure was adopted. Anhydrous HCl (g) was passed through a solution of N-(phthaloyl)-D-alanine (**33**) (1.17 g, 5.32 mmol) in dry ethanol (15 mL) for one hour at 25 °C. The mixture was then heated to reflux for another hour. The solvent was removed *in vacuo* and the resulting slightly yellow oil was purified by flash chromatography (ethyl acetate/hexane 3 : 7). A white solid was obtained (1.09 g, 84%) which had ^1H NMR, IR and mass spectra identical to those of compound **30** prepared using the resin **17b**; $[\alpha]_D$ = +18.5 (c 1, MeOH), $[\alpha]_D$ = +5.2 (c 1, $CHCl_3$); Anal.Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.25; H, 5.47; N, 5.74.

N-(Phthaloyl)-D-alanine (33).

The literature[73] procedure was used to prepare **33**. A mixture of phthalic anhydride (2.34 g, 15.8 mmol) and D-alanine (**32**) (1.40 g, 15.8 mmol) were fused by heating in an oil bath at 150 °C for 20 min. The residue was recrystallized from methanol/water to give 2.67 g (77%) of **33** as white crystals: mp 145-146 °C (lit.[97] mp 150-151 °C); $[\alpha]_D$ +23.2 (c 1.05, MeOH); IR (KBr) 3264, 1777, 1760, 1691, 1611, 1466 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.76 (m, 1H, -COO*H*), 7.88 (m, 2H, Ar-*H*), 7.75 (m, 2H, Ar-*H*), 5.04 (q, 1H, 7.4 Hz, -C*H*), 1.72 (d, 3H, 7.4 Hz, -C*H*$_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.06 (-*C*H_3), 47.29 (-*C*H), 123.63 (Ar), 131.69 (Ar), 134.26 (Ar), 167.39 (O=*C*N*C*=O), 175.31 (-*C*OOH); Anal. Calcd for $C_{11}H_9NO_4$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.00; H, 4.27; N, 6.40.

N,N'-Diphenylcarbodiimide (35).

The polystyrene reagent **17b** (0.934 g, 1.10 mequiv) was suspended in dry THF (25 mL) and a solution of N,N'-diphenylthiourea (**34**) (0.225 g, 0.987 mmol) in THF (3 mL) was added dropwise. The mixture was stirred at 20 °C for 24 h. The resin was filtered and washed successively with methanol (2 x 50 mL) and chloroform (2 x 50 mL). The combined filtrates and washings were concentrated *in vacuo*, and the residue was extracted with petroleum ether to remove product from insoluble triphenylphosphine oxide. Concentration of the extract *in vacuo* gave an oil which was purified by flash chromatography (ethyl acetate/hexane, 3 : 7) to give pure N,N'-diphenylcarbodiimide (35) (78 mg, 41%)[45]: IR ($CHCl_3$ cast) 2140, 2106, 1590, 1487 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 4 H), 7.17 (m, 6 H); exact mass 194.0845 (194.0845 calcd for $C_{13}H_{10}N_2$).

(S)-(+)-Zearalenone Dimethyl Ether (38) and Monomethyl Ether (37).

Acetone was added to a reaction flask containing zearalenone (**36**) (200 mg, 0.628 mmol) and potassium carbonate (0.551 g, 3.78 mmol). Dimethyl sulfate (0.55mL, 0.733 g, 5.81 mmol) was added dropwise and the reaction was heated to reflux for 3 h. The mixture was filtered and the resulting yellow oil was purified by flash chromatography (ethyl acetate/hexane 2 : 8). The dimethyl ether **38** was obtained as a white solid (0.185 g, 85%). An analytical sample was recrystallized from ether: mp 111-112 °C (lit.[81] mp 107-110 °C); $[\alpha]_D$ +23.3 (c 1, MeOH) (lit[84] $[\alpha]_D$ +25 c 1, MeOH); IR ($CHCl_3$ cast) 2940, 1715, 1600, 1265, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, 1H, 3-CH), 6.39 (m, 1H, 1'-CH), 6.35 (m, 1H, 5-CH), 6.00 (m, 1H, 2'-CH), 5.30 (m, 1H, 10'-CH), 3.85 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 2.71 (m, 1H, 5'-C*H*H), 2.35 (m, 3H, 3'-C*H*H, 7'-CH_2), 2.11 (m, 3H, 3'-CH*H*, 4'-C*H*H, 5'-CH*H*), 1.75 (m, 5H, 4'-CH*H*, 8'-CH_2, 9'-CH_2), 1.34 (d, 3H, 11'-CH_3); ^{13}C NMR (APT, 300 MHz, $CDCl_3$) δ 20.07 (11'-C), 21.33 (8'-C), 21.63 (4'-C) , 31.26 (3'-C), 35.20 (9'-C), 37.64 (5'-C), 44.09 (7'-C), 55.46 (C_4-O*C*H_3), 56.01 (C_2-O*C*H_3), 71.19 (10'-C), 97.79 (5-C), 101.39 (3-C), 116.44 (1-C), 129.06 (1'-C), 133.22 (2'-C), 136.66 (6-C), 157.75 (2-C), 161.36 (4-C), 167.61 (12'-C), 211.36 (6'-C); exact mass 346.1781 (346.1781 calcd for $C_{20}H_{26}O_5$).

If the same reaction was done with reflux for only 1.5 h (using 0.100 g, 0.314 mmol of zearalenone), a second product was isolated which was identified as the monomethyl ether **37** (22.0 mg, 21%), in addition to the dimethylated compound **38** (37.8 mg, 35%). For **37**: IR ($CHCl_3$ cast) 2939, 2849, 1701, 1646, 1609, 1574, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.11 (s, 1H, -OH), 7.02 (d, 1H, 1'-CH), 6.48 (d, 1H, 5-CH), 6.40 (d, 1H,3-CH), 5.70 (t, 1H, 2'-CH), 5.02 (m, 1H, 10'-CH), 3.85 (s, 3H, $-OCH_3$), 2.86 (m, 1H, 5'-C*H*H), 2.61 (m, 1H, 7'-C*H*H), 2.38 (m, 1H, 3'-C*H*H), 2.18 (m, 4H, 7'-CH*H*, 5'-CH*H*, 3'-CH*H*, 4'-C*H*H), 1.77 (m, 2H, 8'-CH_2), 1.64 (m, 3H, 9'-CH_2, 4'-CH*H*), 1.40 (d, 3H, 11'-CH_3); ^{13}C NMR (APT, 300 MHz, $CDCl_3$) δ 20.66 (11'-C), 21.06 (4'-C), 22.26 (8'-C), 31.02 (3'-C), 34.77 (9'-C), 36.66 (5'-C), 42.97 (7'-

C), 55.42 (4-C-OCH_3), 73.41 (10'-C), 99.99 (5-C), 103.63 (1-C), 106.19 (3-C), 132.36 (2'-C), 133.31 (1'-C), 143.36 (6-C), 164.07 (2-C), 165.66 (4-C), 171.42 (12'-C), 210.95 (6'-C) ; exact mass 332.1624 (332.1624 calcd for $C_{19}H_{24}O_5$).

Zearalenone Dimethyl Ether Ethylene Ketal (40).

(S)-(+)-Zearalenone dimethyl ether **38** (0.129 g, 0.373 mmol) was dissolved in toluene (20 mL). Ethylene glycol (1.0 mL, 1.11 g, 17.9 mmol) and p-toluenesulfonic acid (8.00 mg, 0.0464 mmol) were added. The mixture was heated to gentle reflux for 6 h using a Soxhlet apparatus containing calcium hydride, to remove the water generated. The layers were separated and the ethylene glycol layer was washed with ether. The combined toluene and ether layers were washed with 10% sodium bicarbonate (20 mL), saturated aqueous sodium chloride (20 mL), and dried with sodium sulfate. The organic layers were concentrated *in vacuo* to give a colourless oil. Recrystallization from ether gave the ethylene ketal **40** (0.150 g, 94 %): mp 100-101 °C (lit.[84] mp 101-103 °C); IR ($CHCl_3$ cast) 1721, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.62 (d, 1H, 1'-CH), 6.36 (m, 3H, 5-C*H*, 3-C*H*, 2'-C*H*), 5.24 (m, 1H, 10'-C*H*), 3.95 (s, 4H, -OCH_2CH_2O-), 3.84 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3). 2.40 (m, 1H), 2.14 (m, 1H), 1.70 (m, 10H), 1.36 (d, 3H, 7Hz, 11'CH_3); exact mass 390.2042 (390.2043 calcd for $C_{22}H_{30}O_6$).

(S)-2,4-Dimethoxy-6-((E)-6-dioxalonyl-10-hydroxy-1-undecenyl)benzoic Acid (41).

Compound **40** (0.143 g, 0.366 mmol) was dissolved in dimethylsulfoxide (15 mL) and stirred under argon. To this was added 20% aqueous NaOH (2 mL) and the mixture was heated gently to reflux for 4 h. The resulting yellow solution was cooled to 10 C, acidified with dil HCl, and extracted with chloroform (4 x 10 mL). The organic layer was concentrated *in vacuo* to give pure **41** as an oil (0.142 g, 95%):[84] IR ($CHCl_3$ cast) 3300, 2033, 1713, 1600, 1579 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 6.95 (m, 2H, -O*H*), 6.56

(m, 2H, 3-C*H*, 1'-C*H*), 6.40 (m, 2H, 2'C*H*, 5-C*H*), 6.10 (m, 1H, 10'-C*H*), 3.90 (m, 10H, -OCH_3, -OCH_2CH_2O-), 2.45 (m, 2H), 2.24 (m, 4H), 1.60 (m, 6H), 1.20 (d, 3H, 11'-CH_3); POSFAB MS (glycerol) 407 (M^+).

(S)-2,4-Dimethoxy-6-((E)-10-hydroxy-6-oxo-1-undecenyl)benzoic Acid (42).

A solution of **41** in THF (5 mL) and 2.2 N perchloric acid (5 mL) was stirred for 2 h at 25 °C. Water (20 mL) was added and the mixture was extracted with chloroform (3 x 20 mL). The organic layer was washed with saturated sodium chloride (aqueous) and dried over sodium sulfate to give **42**: IR ($CHCl_3$ cast) 3300, 2034, 1713, 1600, 1579 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.78 (m, 2H, -O*H*), 6.62 (m, 2H, 3-C*H*, 1'-C*H*), 6.38 (m, 2H, 2'C*H*, 5-C*H*), 6.10 (m, 1H, 10'-C*H*), 3.90 (m, 10H, -OCH_3, -OCH_2CH_2O-), 2.46 (m, 2H), 2.24 (m, 4H), 1.68 (m, 6H), 1.20 (d, 3H, 11'-CH_3); POSFAB MS (glycerol) 363 (M^+).

(R)-(-)-Zearalenone Dimethyl Ether (43) .

The polystyrene resin **17b** (67 mg, 0.12 mequiv) was suspended in dry THF (5 mL) and a solution of triphenylphosphine (26 mg, 0.10 mmol) in THF (2 mL) was added. A solution of the hydroxy acid **42** (26 mg, 0.070 mmol) in THF (2 mL) was added at 25 °C, and the mixture was stirred 48 h. The resin was filtered and washed with THF (5 mL), and the combined filtrate and washings were concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane, 3 : 7) of the residue gave 10 mg (42%) of (R)-(-)-zearalenone dimethyl ether **43**: mp 111-112 °C (c.f. for **38**: mp 111-112 °C); $[\alpha]_D$ -23.2 (c 1, MeOH) (c.f. for **38**: $[\alpha]_D$ +23.3 (c 1, MeOH)) ; exact mass 346.1772 (346.1781 calcd for $C_{20}H_{26}O_5$).

Benzophenone Oxime (44).

The literature procedure[98] was employed. Benzophenone (25.0 g, 0.137 mol) was treated with hydroxylamine hydrochloride (15.0 g, 0.216 mol) in 95% ethanol (50 mL) and water (10 mL). Sodium hydroxide pellets (28.0 g, 0.700 mol) were added in portions with stirring. When addition was complete, a reflux condenser was attached to the reaction flask and the mixture was boiled for 5 min. The mixture was cooled to room temperature and poured into a solution of conc HCl (75 mL) in water (500 mL). A white precipitate was obtained which was filtered and washed with cold water. The product was dried in an oven at 40 °C to give 27.0 g (99%) of pure benzophenone oxime **44**: mp 142.5-143.5 °C (lit.[98] mp 142-143 °C); IR (Nujol mull) 3240, 1635, 1442, 920 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.40 (m, 10H, Ar-*H*), 9.51 (m, 1H, -O*H*); exact mass 197.0847 (197.0841 calcd for $C_{13}H_{11}NO$).

4-(2-Oxo-4,5-diphenyl-1,3-oxazol-3-yl)butyric Acid (45).

The procedure of Sheehan and Guziec[99] was employed. γ-Aminobutyric acid (0.217 g, 2.10 mmol) was dissolved in a 20% solution of tetramethylammonium hydroxide in ethanol (1.0 mL, 2.10 mmol). The solution was concentrated and dried *in vacuo*. The resulting solid was dissolved in dimethylformamide (10.0 mL). Dioxolone **47** (0.503 g, 2.11 mmol) was added to give an intense yellow-green colour which turned yellow and then colourless in 2-3 minutes. The mixture was stirred at 20 °C for 2.5 h. The solution was diluted with ethyl acetate (50 mL) and washed with water (3 x 25 mL). It was dried over sodium sulfate, concentrated, and dried *in vacuo*. A pale yellow solid (0.660 g) was obtained. Trifluoroacetic acid (4.0 mL) was added and the mixture was stirred at 20 °C for 2 h. The acid was removed *in vacuo* and the residue was diluted with dichloromethane (25 mL). This was washed with water (2 x 10 mL), dried over sodium sulfate, and concentrated *in vacuo*. The pure product **45** was obtained as a yellow solid (0.603 g,

89%). This was recrystallized from ethyl acetate/hexane to give 0.512 g (75%): mp 138-140 °C; IR ($CHCl_3$ cast) 3060, 3000, 1755, 1711, 1600 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 9.10 (m, 1H, -O*H*), 7.48 (m, 5H, Ar*H*), 7.20 (m, 5H, Ar*H*), 3.55 (t, 2H, 7 Hz, -C*H*$_2$COOH), 2.30 (t, 2H, 7Hz, -C*H*$_2$N), 1.85 (m, 2H, -CH_2C*H*$_2CH_2$); exact mass 323.1160 (323.1158 calcd for $C_{19}H_{17}NO_4$); Anal. Calcd (for $C_{19}H_{17}NO_4$) C, 70.58; H, 5.30; N, 4.33. Found: C, 70.62; H, 5.10; N, 4.24.

(S)-3-[(1-oxo-3-carboxybutyl)-4-benzyloxazolidin-2-one (46).

This was prepared according to the procedure by Evans et al.[100] (S)-(-)-4-Benzyl-2-oxazolidinone (**48**) (Aldrich) (0.885 g, 4.99 mmol) was dissolved in THF (5.0 mL) and cooled to 0 °C. n-Butyllithium (1.47M, 4.0 mL) was added, and the mixture was stirred for 5 min. Succinic anhydride (0.50 g, 5.00 mmol) was dissolved in THF (7.0 mL) and added to the mixture which was then stirred for 5 min. A white precipitate was obtained. The solvent was removed *in vacuo*. Ammonium chloride (5% solution, 5.4 mL) was added and the solution was acidified to pH 2 using 6N HCl. This was extracted with ethyl acetate (3 x 20 mL). The ethyl acetate layer was extracted with 5% sodium carbonate solution. The aqueous layer was acidified with 6N HCl and extracted with $CHCl_3$. The chloroform layer was dried over sodium sulfate and concentrated *in vacuo*. A yellow oil was obtained (0.908 g, 65%) which was further purified by silica gel chromatography (elution with chloroform and methanol). Compound **46** was obtained as an oil (0.831 g, 60%): IR ($CHCl_3$ cast) 3100, 1781, 1703, 1389 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 9.42 (m, 1H, -O*H*), 7.28 (m, 5H, Ar*H*), 4.70 (m, 1H, -CH_2C*H*CH_2), 4.20 (d, 2H, 8Hz, -OC*H*$_2$CH), 3.25 (m, 2H, -C*H*$_2$), 2.80 (m, 2H, -CH_2); exact mass 277.0946 (277.0951 calcd for $C_{14}H_{15}NO_5$).

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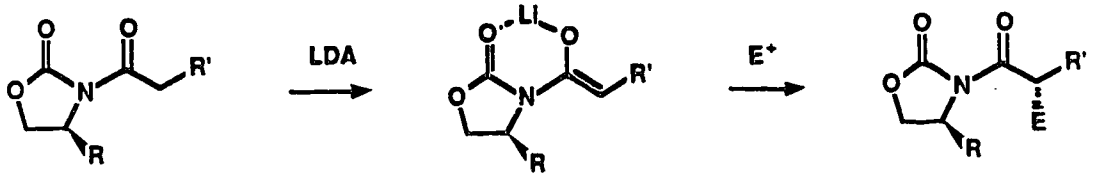
APPENDIX 1

The most recent approaches to the synthesis of α-amino acids rely on the stereospecific construction of one or more bonds to the α-carbon.[101] Recent studies by Evans and co-workers[102] have demonstrated that the enolates of chiral carboximides (Scheme 35) react with electrophiles in a highly diastereoselective fashion to give predominantly one of the two possible diastereomeric products.

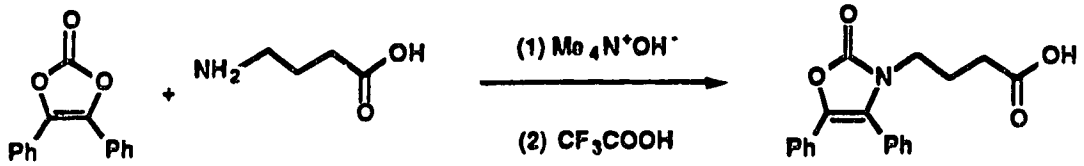
Scheme 35.



This is mainly due to three factors.[102] The steric interactions between the R and R' groups lead to predominant formation of the Z enolate. Chelation of Li^+ with the carbonyl and enolate oxygens inhibits rotation around the nitrogen-carbon bond and fixes the conformation of the molecule. Finally, the steric bulk of the R group hinders the approach of an electrophile from the *re* face (R' = alkyl). Thus, attack is essentially limited to the *si* face and only one diastereomer is obtained.

In the course of this work, an oxazolone **45** and a chiral carboximide **46** were prepared for use in asymmetric synthesis of amino acids. Reaction of γ-aminobutyric acid with the cyclic carbonate **47** using the method of Sheehan et al.[99] gave the oxazolone **45** in 75% yield (Scheme 36).

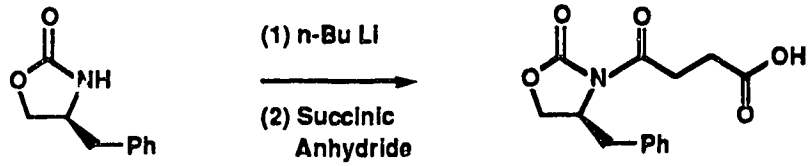
Scheme 36.



47 45

The carboximide **46** was prepared by the reaction of the lithium salt of the chiral oxazolidinone **48** with succinic anhydride[100] (Scheme 37).

Scheme 37.



48 46

These compounds are useful synthetic intermediates for preparation of a wide range of α-amino acids[64] including α-hydrazino acids.[101f]