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Development of a Chiral Aminating Reagent and Amination Studies on Chiral and Achiral Molecules

by

Aubrey Julian Mendonca 

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

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THE UNIVERSITY OF ALBERTA

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Supervisor

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.....

Date: 27th June 1989

To Mum and Dad

Abstract

Steroid molecules are known to have a rigid skeleton, and this characteristic was explored in bridging the hydroxyl groups in chenodeoxycholic acid (**1**) and deoxycholic acid (**2**) in order to form a new chiral aminating reagent. The carboxylic acid in the side chain was protected as the diethylamide to yield **3** and **4**. Initial studies involved the formation of carbon bridges between the two hydroxyl groups.The hydroxyl groups in chenodeoxycholic acid were bridged with glutaryl chloride to yield **7**, whereas in deoxycholic acid, the bridge formed with succinyl chloride to yield **8**. All attempts to form the -O-CO-NH-NH-CO-O- linkage were unsucessful after the activation of the hydroxyl groups with phenyl chloroformate, followed by reaction with hydrazine, but instead only the mono hydrazides at the C-3 position of the steroid nucleus were obtained, in **11** and **12** respectively.

Other molecules used to form the chiral aminating reagent included menthol (**13**), borneol (**25**), and isoborneol (**32**). Amination of ethyl phenylacetate (**19**) and diethyl succinate (**20**) with dimenthyl azodicarboxylate (**18**), and dibornyl azodicarboxylate (**28**), often led to a mixture of diastereomers as seen by variable temperature ^{1}H NMR spectra. Further more, these products could not be cleaved to their parent hydrazino acids. Amination with diisobornyl azodicarboxylate (**35**) also led to a mixture of diastereomers, but these can be cleaved to produce the desired α-hydrazino acids.

Amination of the enolates of the oxazolidinone carboximides **38** and **39** with **35** led to single diastereomers, **40** and **41**, respectively. The oxazolidinone moiety was cleaved with $LiOH/H_2O_2$ and the products were methylated to the corresponding methyl esters **43** and **44**. The individual diastereomer structure was confirmed by variable temperature ^{1}H NMR spectra of their methyl esters and an independent synthesis.

Amination of achiral amides **49** and **51** with **35** led to a 1:1 mixture of diastereoisomers **50** and **52** respectively, which can be cleaved directly to the parent hydrazino acids by heating with 6N HCl.

Acknowledgements

I would like to thank my supervisor, Dr. John C. Vederas, for his guidance and encouragement during my studies. Appreciation is extended to all members of the research group, especially Dr. Paul Reese, Dr. Yuko Yoshizawa, Mr. William Sherwin, and Mrs. Patricia Lane-Bell for informative discussions, and to Mr. S. C. Feng for technical assistance. A special word of gratitude goes out to Dr. Yuko Yoshizawa for patiently running and acquiring the numerous variable temperature ^1H NMR spectra. All members of the spectral and technical services in the Department of Chemistry are gratefully acknowledged for proficient and expeditive help rendered. Finally I would like to thank most of all my parents, brothers, and sisters, for all the help, support, and encouragement given during the course of all my studies.

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List of Abbreviations

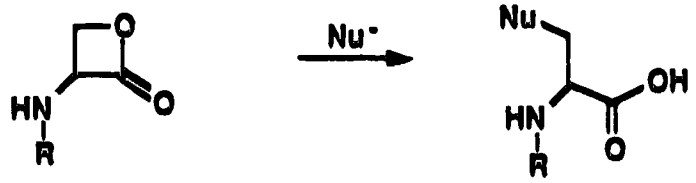
Ac	acetyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
CBZ	benzyloxycarbonyl
DMAP	dimethylaminopyridine
DMF	dimethylformamide
EI	electron impact ionisation
Enz	enzyme
Et	ethyl
FAB	fast atom bombardment
HMDS	hexamethyldisilazane
IR	infra red
LDA	lithium diisopropylamide
Me	methyl
MOM	methoxy methyl
MS	mass spectrometry
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
PLP	pyridoxal phosphate
iPr	isopropyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

INTRODUCTION

Although the twenty common L-α-amino acids are found mainly in proteins and peptides, the bulk of the remaining naturally occurring amino acids, both the L and D isomers, occur in lower organisms and plants, either in free form or as constituents in peptides.[1] Amino acids, have found a wide variety of uses as antibiotics,[1-7] enzyme inhibitors,[8-12] synthetic intermediates,[13,14] and biochemical probes.[15]

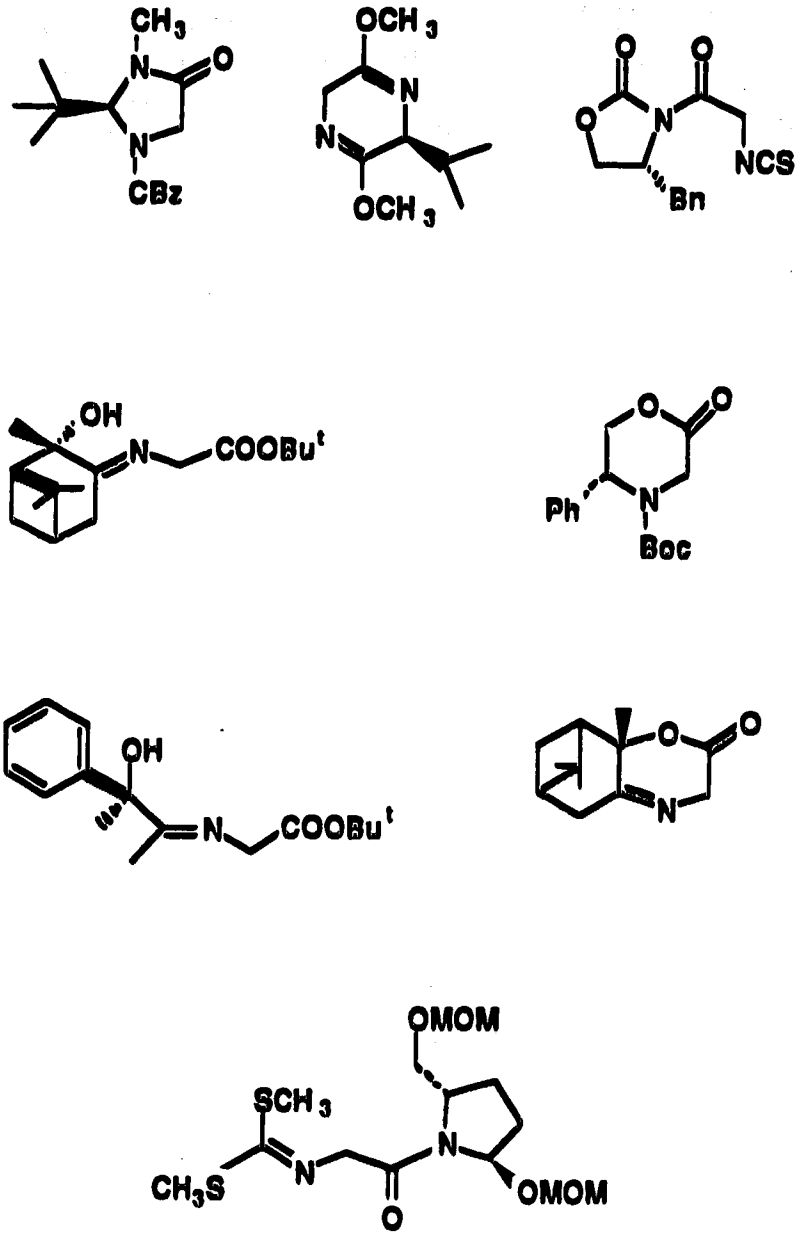
The importance of these compounds, as well as their wide potential in the pharmaceutical industry, has recently led to development of a large number of methods for their synthesis in the enantiomerically pure form.[16-29] For example, a recent method which involves formation of a carbon-carbon bond at the β position of the amino acid, is the opening of N-protected α-amino-β-lactones, (Figure 1),[30-33] to give enantiomerically pure β – substituted α - amino acid derivatives.

Figure 1: Opening of β-lactones



Other approaches generate a carbon-carbon bond at the α-position by alkylation of chiral glycine synthons.[22,25,34-46] These synthons provide access to both natural and unnatural non-protein amino acids with special side chains; for example, isotopically labelled amino acids and D - amino acids are readily available from such precursors. Some chiral glycine derivatives used in amino acid synthesis are shown in Figure 2.

Figure 2: Chiral glycine derivatives that are used in amino acid synthesis[34-46]



An alternative approach involves the formation of the carbon - nitrogen bond of the amino acid by transamination[47-49] of α - keto acids (Figure 3), or amination[50-55] of chiral

enolates with achiral azodicarboxylates to hydrazino acid derivatives followed by cleavage to the amino acid (Figure 4).

Figure 3: Example of an amino acid by transamination with a model enzyme

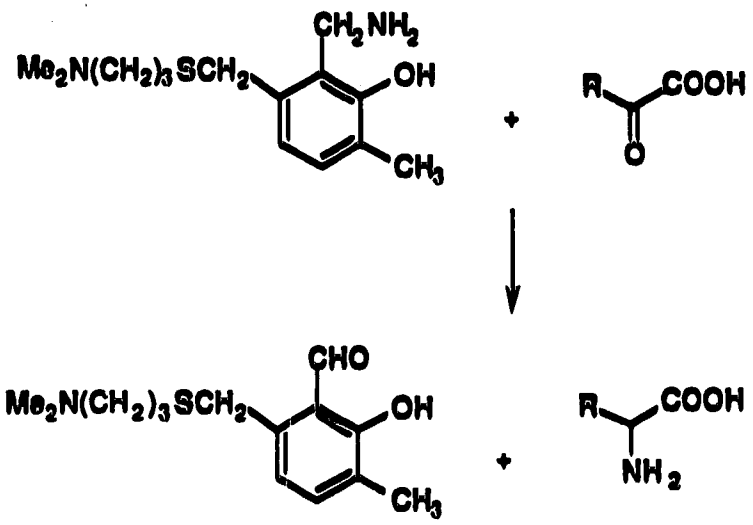
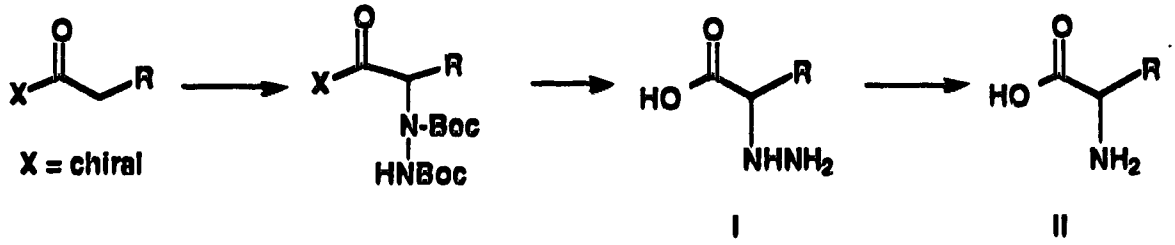


Figure 4: Amination with an achiral azodicarboxylate reagent Boc-N=N-Boc



The latter conversion involves either catalytic hydrogenolysis[56] or nitrosation and reduction[57] of the free α-hydrazino carboxylic acids (I) to the α-amino acids (II).

Earlier syntheses of α-hydrazino acids, prior to the electrophilic amination of chiral enolates, usually employed enantiomerically pure α-amino acids. However such methods are often tedious and lengthy procedures that result either in low yields or loss of optical activity.[56-71]

α-Hydrazino carboxylic acids are important due to their physiological properties,[72-75] antibiotic activity,[76-78] and use as β-lactam[79-82] and peptide analogue building blocks.[83-86] They are also very strong competitive inhibitors of certain enzymes which metabolise amino acids,[58,76,87-99] especially the pyridoxal phosphate (PLP) dependent enzymes. The mechanism of pyridoxal phosphate (PLP) dependent enzymes has been studied in great depth.[100-102] The PLP cofactor, which acts as an electron sink, is present as an imine adduct with the ε-amino group of a lysine residue in the enzyme active site.[100] The PLP enzymes usually act at the α-position of the amino acid to catalyse either epimerisation, transamination, or decarboxylation. In epimerisation and transamination, the α– carbon - hydrogen bond is cleaved, whereas in decarboxylation (Figure 5), the carboxyl group is cleaved. Possible inhibition by an α-hydrazino carboxylic acid could involve formation of a hydrazone intermediate (Figure 6). This intermediate is incapable of delocalization of electrons at the α-carbon and is less susceptible to hydrolysis, thus blocking the normal mode of enzyme action .

Figure 5: Mechanism for pyridoxal phosphate dependent enzyme decarboxylation.

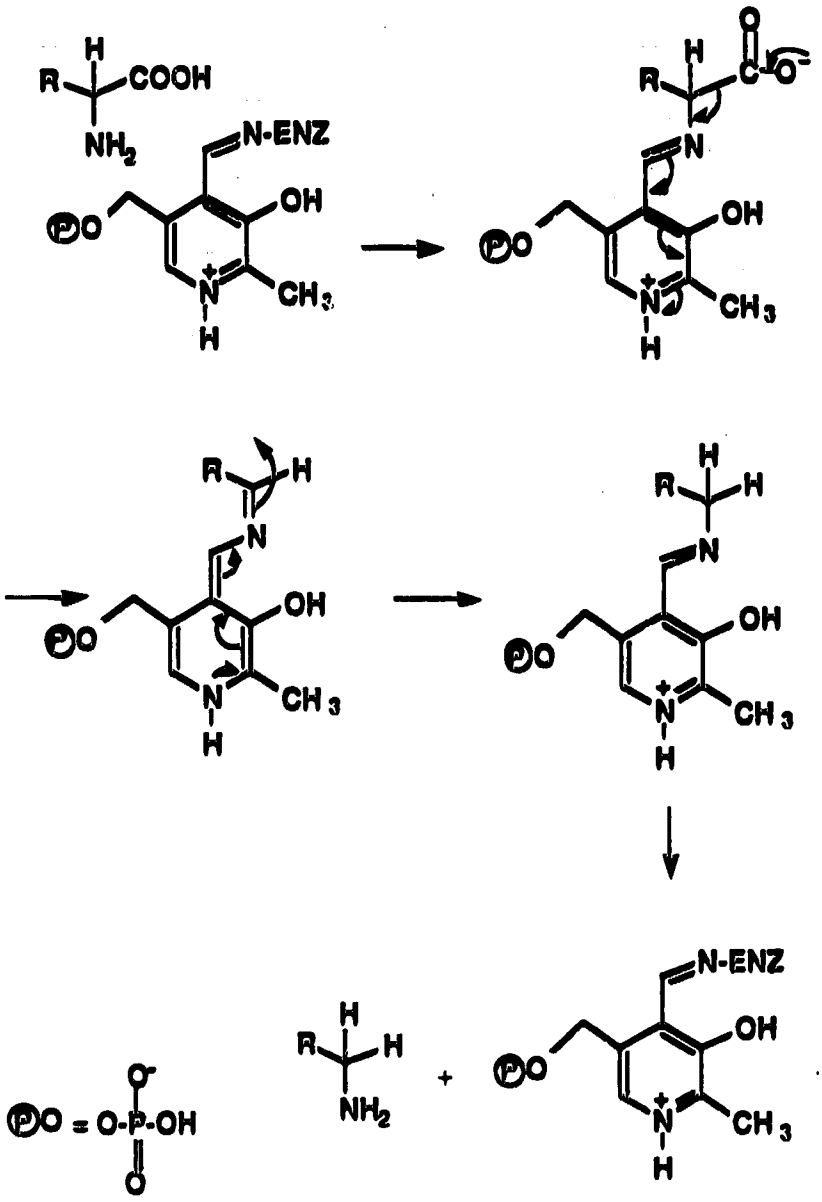
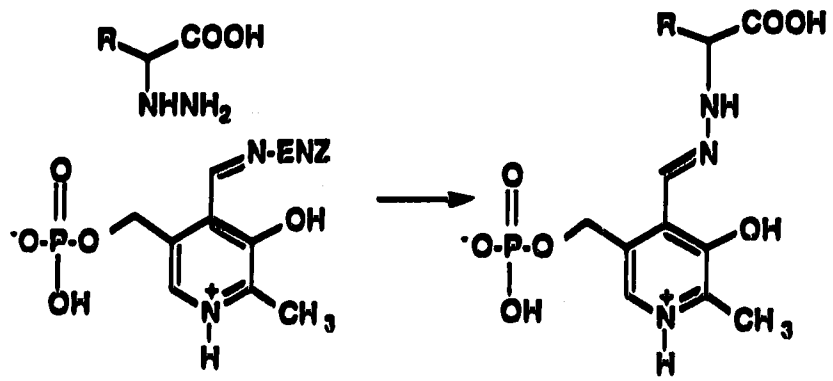
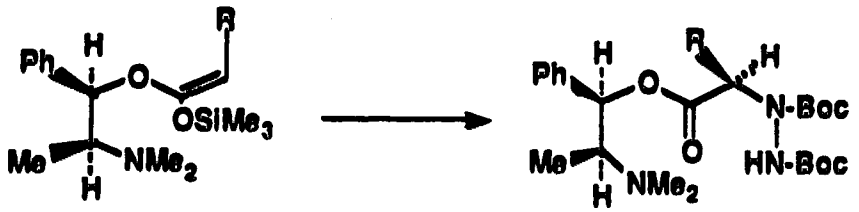


Figure 6: Proposed mechanism of inhibition of the pyridoxal phosphate (PLP) dependent enzymes.



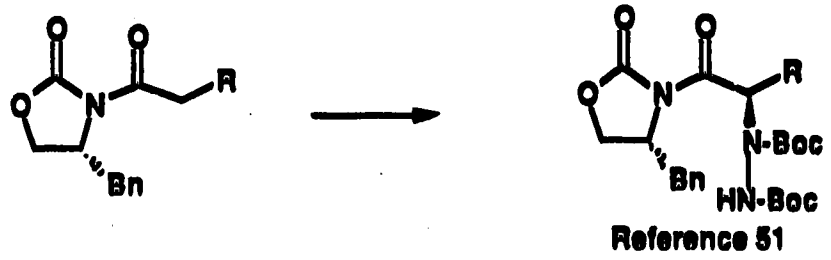
Dialkyl azodicarboxylate has long been known to be highly reactive towards nucleophiles, and thus as a potential reagent in the synthesis of α-hydrazino acids.[50-55,103-111] Recent studies[50-55] have used these compounds as a source of electrophilic nitrogen in reactions with chiral enolates. (Figure 7). If the enolate possess a chiral center, significant diastereoselection can be observed.

Figure 7: Recent methods of amination of chiral enolates.



Reference 50

Figure 7: Recent methods of amination of chiral enolates continued



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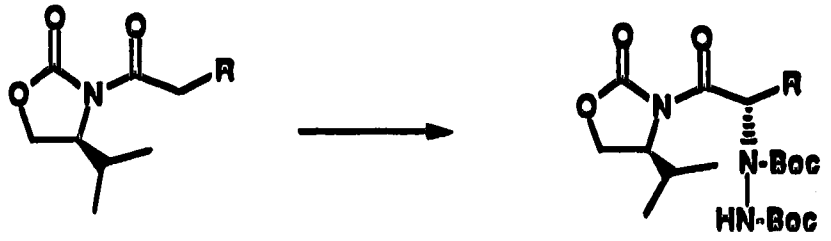

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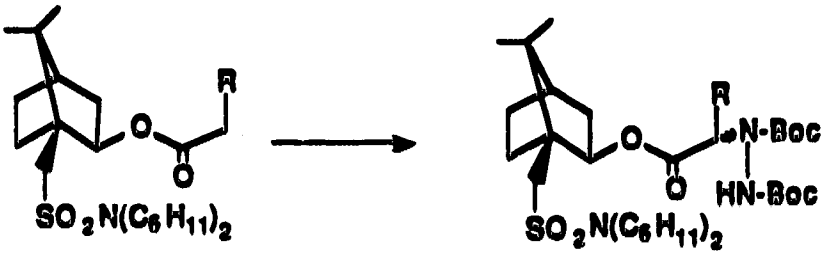


Reference 53

The main drawback with the above procedures is that asymmetric induction is less than 100% and the resulting mixture is often difficult to separate into its component diastereomers. The development of an accessible and stable chiral dialkyl azodicarboxylate, which would form only one diastereomer upon reaction with an enolate, is highly desirable. This would afford a facile stereospecific synthesis of α-hydrazino carboxylic acids and amino acids.

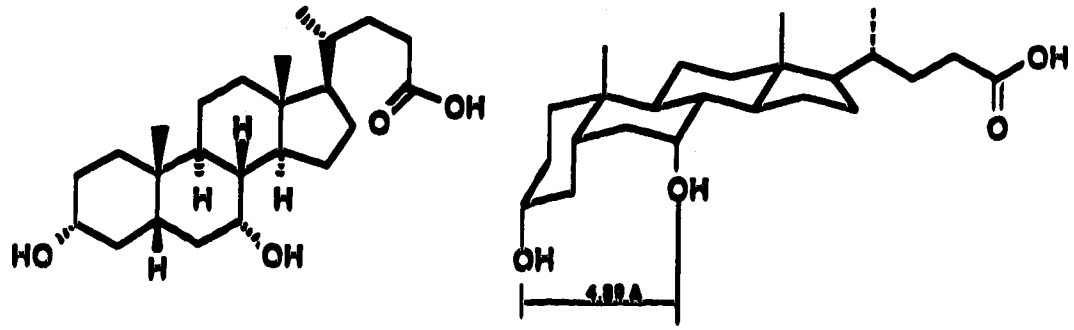
The present work describes studies on generation of such aminating reagents and examines reactions of chiral dialkyl azodicarboxylates with achiral and chiral enolates.

RESULTS AND DISCUSSION

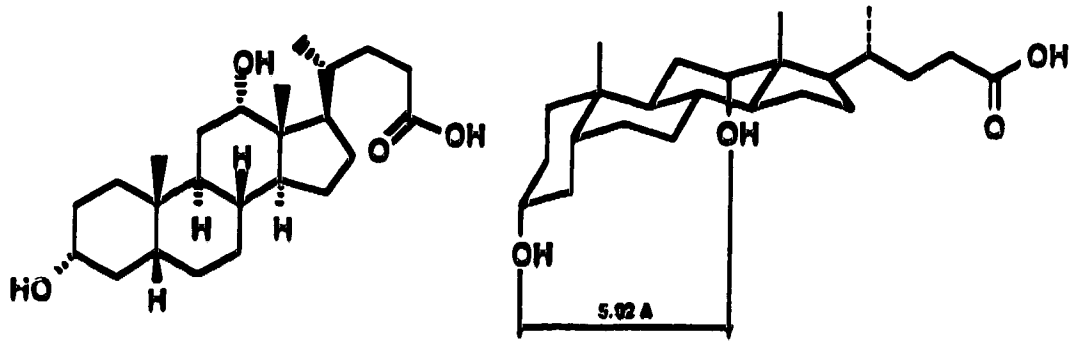
Dialkyl azodicarboxylates are reactive towards a variety of molecules like ester and amide enolates, aromatic compounds, olefins, diazo compounds, aldehydes, and ketones.[50-55, 103-111] Since reactions of enolates of chiral molecules with achiral azodicarboxylates were known to proceed in a diastereoselective manner,[50-55] we decided to change the achiral azodicarboxylate to a chiral moiety and study the effect on stereochemical purity of the amination product. The main criteria in choosing the appropriate chiral starting material is that it be inexpensive, readily available in optically pure form, and be easily deprotected after amination to yield the α-hydrazino carboxylic acid.

Steroids appear to be ideal starting materials which satisfy the above criteria, and have a rigid structure. Potentially they could provide the skeleton for the formation of a azodicarboxylate bridge between the hydroxyl substituents. Some steroids also possess a side chain at C-17 which potentially provides a linking arm for the attachment of the molecule to be aminated or for connection to a solid support. Recent work by Breslow et al.[112-115] on the use of steroid templates in remote chlorinations provides some precedent for the use of such rigid molecules. Two bile acids were chosen for this study, chenodeoxycholic acid (**1**) and deoxycholic acid (**2**), because they are commerically available, inexpensive, and can be selectively modified. Their proton and carbon assignments were also known.[133] The distance between the two hydroxyl groups was shown by X-ray studies to be 4.89 Angstroms in **1**[116] and 5.92 Angstroms in **2** (Figure 8).[117] Molecular models suggest that it may be possible to bridge the two hydroxyl groups by a -CO-NH-NH-CO- linkage in both **1** and **2**.

Figure 8: Stuctures of the bile acids



CHENODEOXYCHOLIC ACID 1

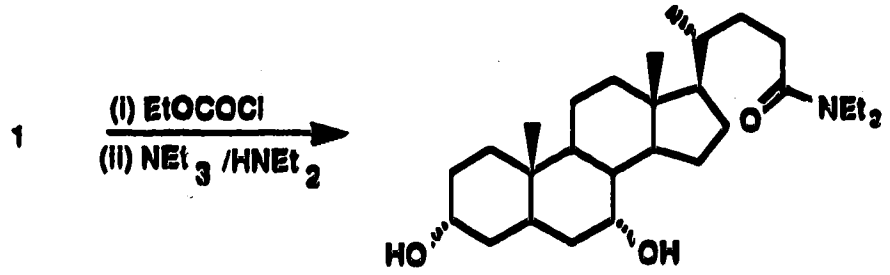


DEOXYCHOLIC ACID 2

Prior to making an attempt to bridge the two hydroxyl groups, the acid group in the side chain was protected as an amide.[118-120] The activation of the carboxylic group can be achieved by formation of either a mixed anhydride, an acid chloride, or a p-nitrophenyl ester.[120] Although they give good yields the latter two procedures are quite laborious. The mixed anhydride method[120] proved to be the most facile with satisfactory yields. The carboxylic acid groups in the side chain in chenodeoxycholic acid (1) and

deoxycholic acid (2) were activated with ethyl chloroformate[120] and allowed to react with diethylamine to yield the amides 3 and 4 in 90% and 84% yields, respectively (Scheme 1).

Scheme 1:



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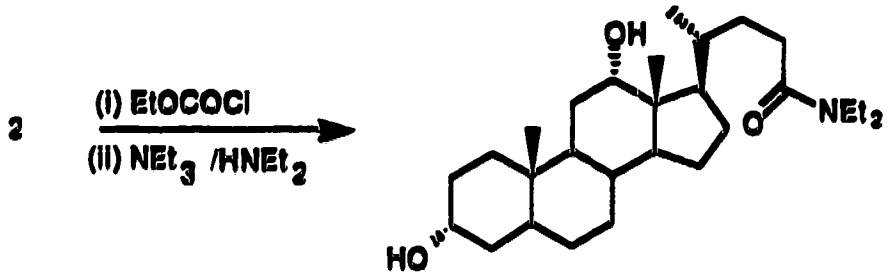
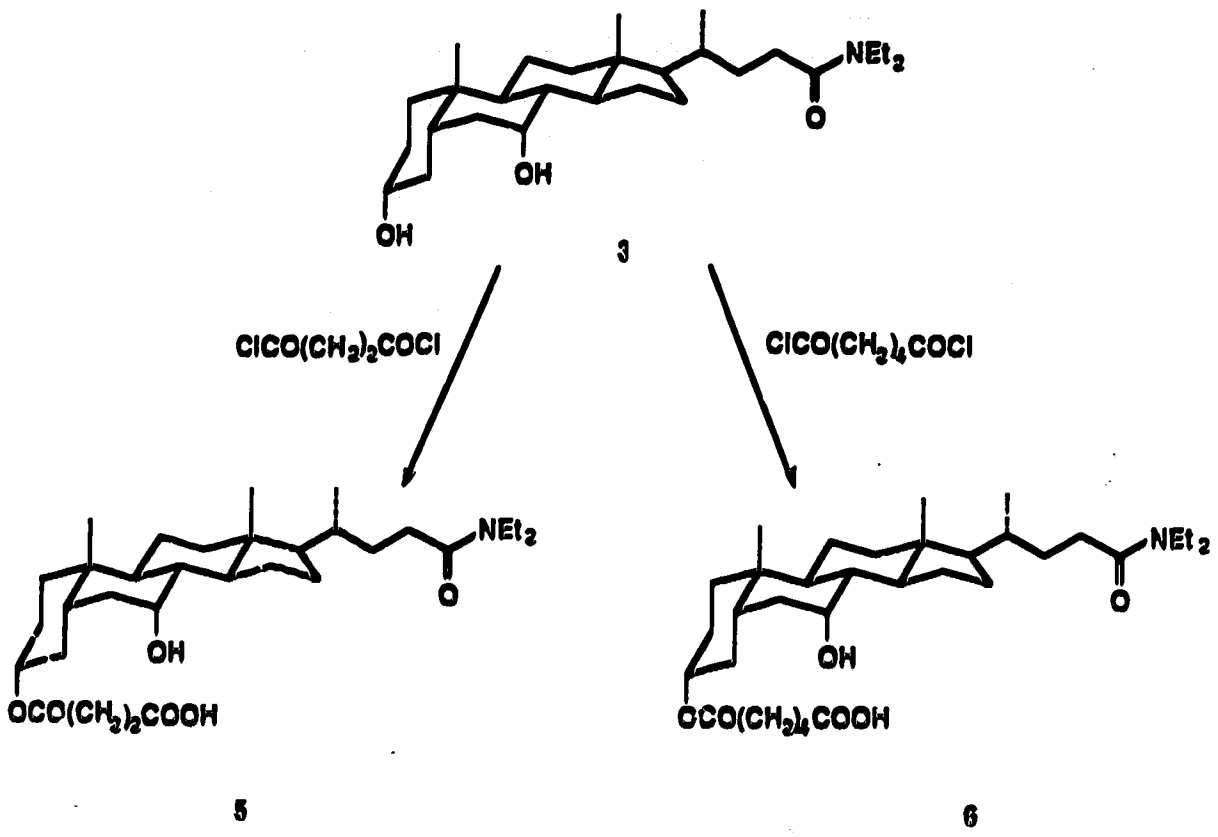


4

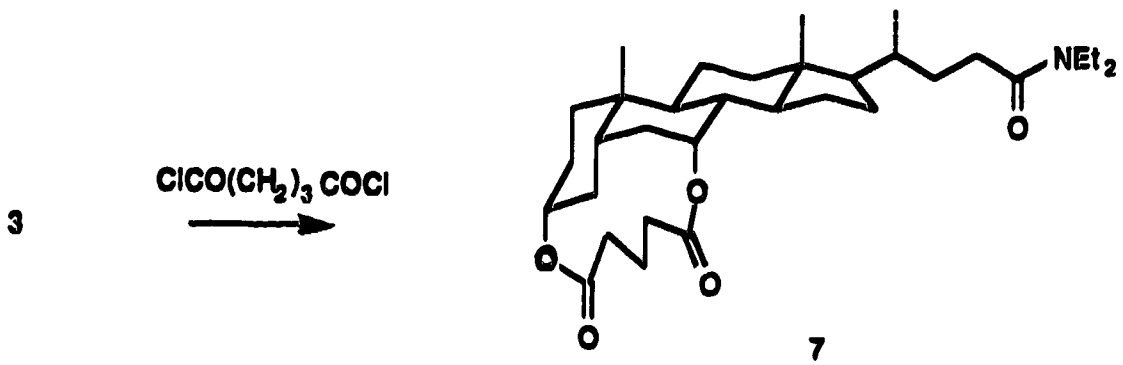
Initial model studies involved the bridging of the two hydroxyl groups with carbon chains. Reaction of N,N-diethylchenodeoxycholamide (3) with succinyl chloride in the presence of pyridine at 0 °C followed by aqueous workup, produces 5 in 82% yield. Similarly adipoyl chloride also fails to bridge the hydroxyls and affords 6 in 26% yield (Scheme 2).

Scheme 2:



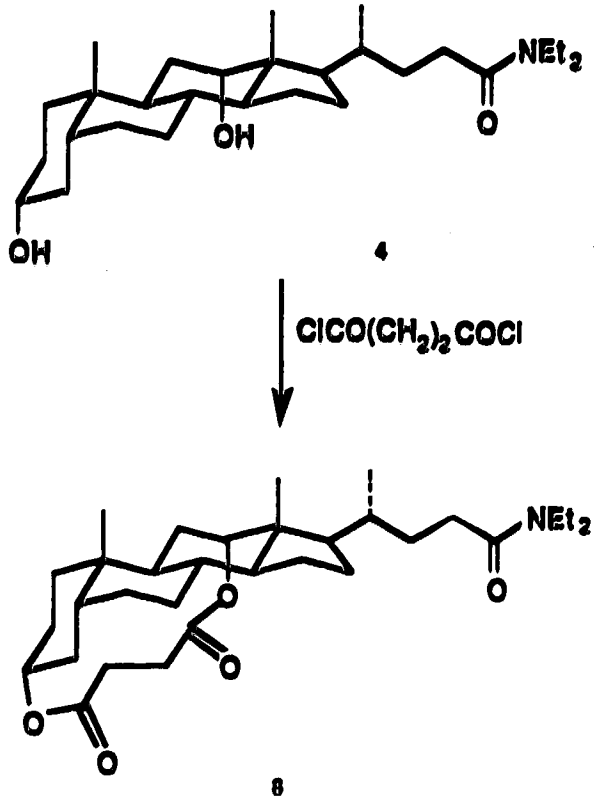
However, successful carbon bridging could be achieved with glutaryl chloride to yield **7** in 66% yield. (Scheme 3)

Scheme 3:



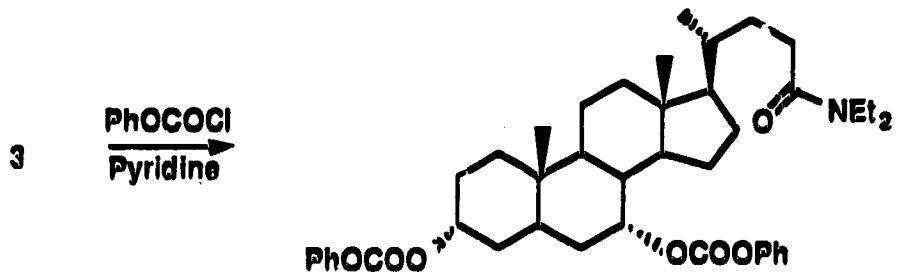
Interestingly N,N-diethyldeoxycholamide (4) formed the desired carbon bridge with succinyl chloride to yield 8 in 46% yield, under the same conditions as those used to prepare 7, the chenodeoxycholic acid derivative (Scheme 4). These results demonstrate that the separation of the hydroxyl groups on the rigid steroid skeleton places stringent limits on bridging groups. Presumably successful linking of a bifunctional moiety can be achieved only if a favorable conformation can be attained in the product. Hence chains which are shorter (succinyl) or longer (adipoyl) than ideal (glutaryl) fail to bridge C-3 and C-7 hydroxyls in 3. However, the more flexible carbon containing chains are not really good models for a more rigid azodicarboxylate residue.

Scheme 4:

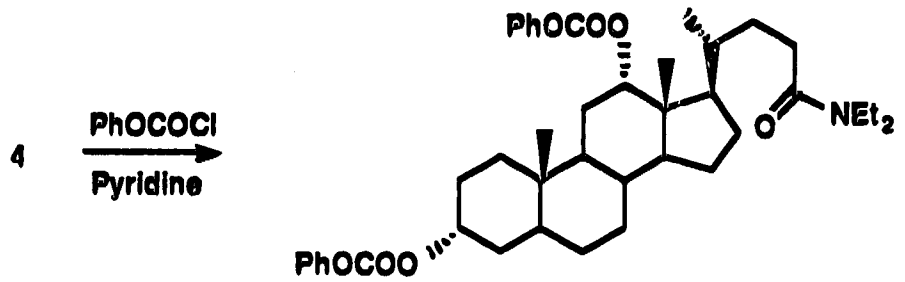


Having been able to successfully bridge the hydroxyl groups in **3** and **4** with carbon chains, formation of the -CO-NH-NH-CO- linkage was examined. Earlier studies[121-124] had shown that the C-3 hydroxyl group of cholic acids is the most reactive, and that reaction with excess ethyl chloroformate in pyridine yields only the 3-carbethoxyl derivative. Combination of the procedures of Fieser et al.[125] and Hansen et al.[126,127] using excess phenyl chloroformate activates the hydroxyl groups of **3** and **4** to afford the bisphenyl carbonates **9** and **10** in 99% and 75% yield, respectively (Scheme 5).

Scheme 5:



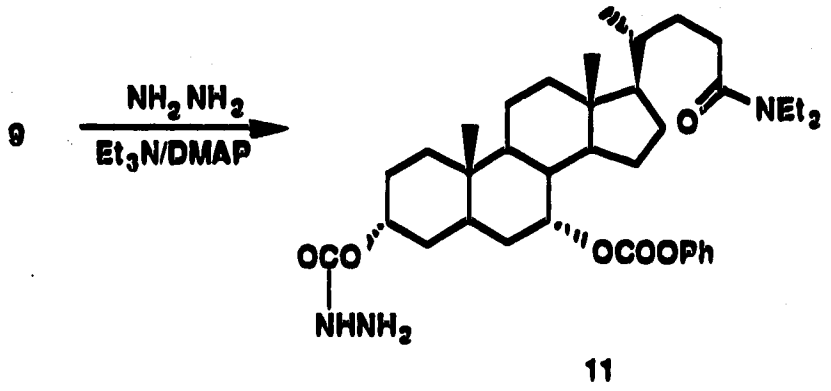
9



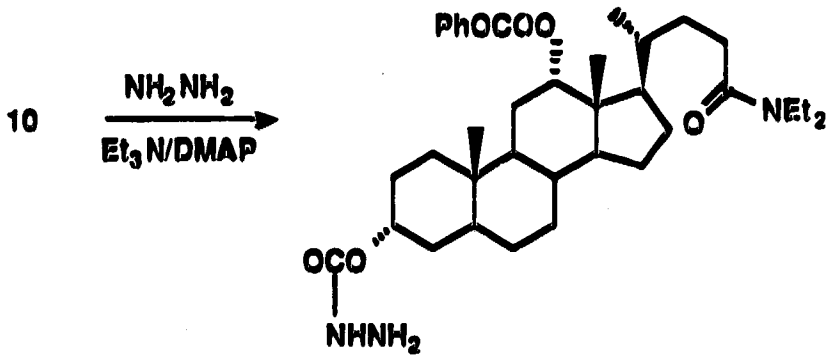
10

Unfortunately repeated attempts to bridge the carbonates in **9** and **10** with hydrazine failed, and only gave reaction at the C-3 substituent to generate the mono hydrazides **11** and **12** in 92% and 71% yield respectively (Scheme 6).

Scheme 6:



11



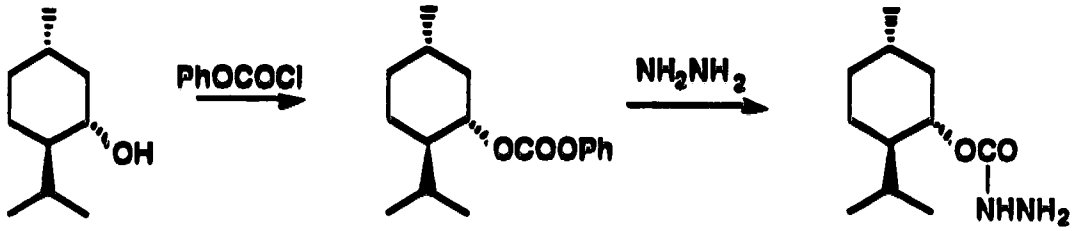
12

Models of the intermediate carbonates suggest that the bulky groups at C-3 and C-7/C-12 are directed away from each other in order to reduce steric interaction. This coupled with the rigidity of the steroid nucleus and the requirement for planarity of the amide (urethane) functionality prevent the formation of the required NH-NH bridge between the two carbonate groups in **9** and **10**. The strict conformational requirement is

apparent from the carbon bridging experiments wherein a five carbon link is necessary in N,N-diethylchenodeoxycholamide (3) whereas only four carbons are necessary to form the bridge in N,N-diethyldeoxycholamide (4), even though the latter has a greater distance between the two hydroxyl groups.

Since the intramolecular hydrazino linkage could not be achieved, connection of two identical chiral molecules using an azodicarboxylate bridge was examined. The first chiral auxiliary chosen is inexpensive D-menthol (13) which is readily available in enantiomerically pure form.[128] Excess phenyl chloroformate activates the hydroxyl group to yield the phenyl menthyl carbonate (14) in 80% yield, but reaction of two molecules of 14 with one molecule of hydrazine at 20 °C for two day produces only menthyl carbazate (15) in 84% yield (Scheme 7).

Scheme 7:

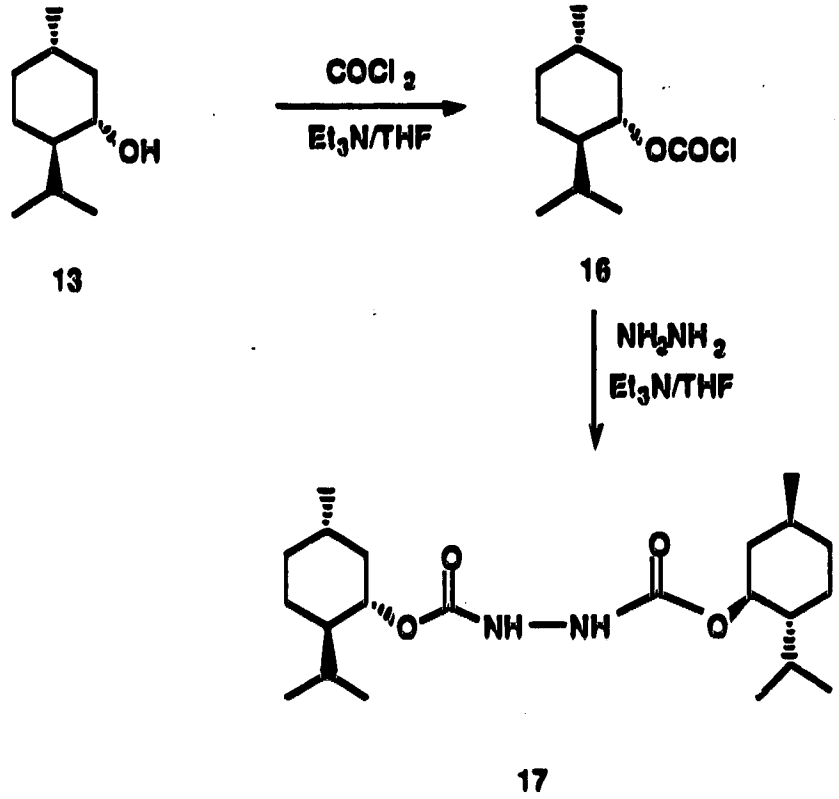


13 14 15

Failure to form the hydrazodicarboxylate may be due to steric intereference and lack of reactivity of the carbonate group.

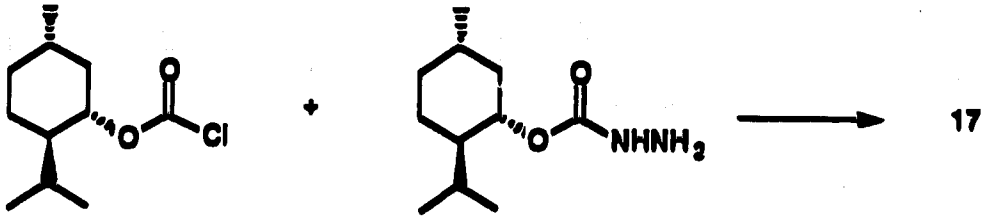
To overcome this problem, the chloroformate **16** was formed with phosgene[129] and triethylamine at 20 °C. The resulting triethylamine hydrochloride salt was filtered and the filtrate was concentrated. Due to the unstable nature of **16**, this compound is not isolated, but treated directly with hydrazine at 0 °C to produce dimenthyl hydrazodicarboxylate (**17**) in 41% yield along with recovered menthol (Scheme 8).

Scheme 8:



Menthyl chloroformate (**16**) also reacts with the menthyl carbazate (**15**) to form **17** in 76% yield (Scheme 9). The latter procedure gives a better yield, probably because the intermediate carbazate is pure.

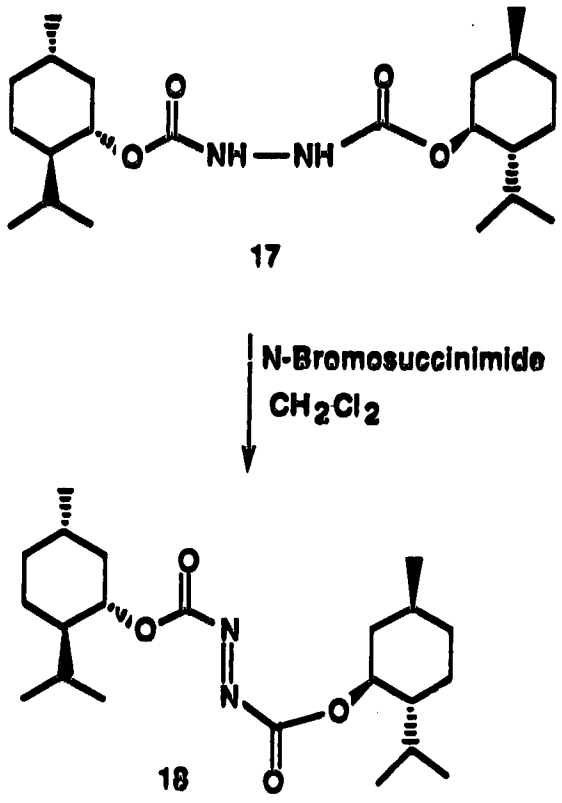
Scheme 9:



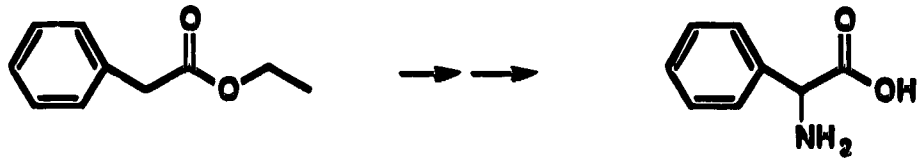
16 15

Purified N-bromosuccinimide[130] oxidises[131] the hydrazo group in **17** to form dimenthyl azodicarboxylate (**18**) in 86% yield (Scheme 10). The complex menthyl resonances in the ^1H NMR spectrum of this product were assigned according to Turner.[132]

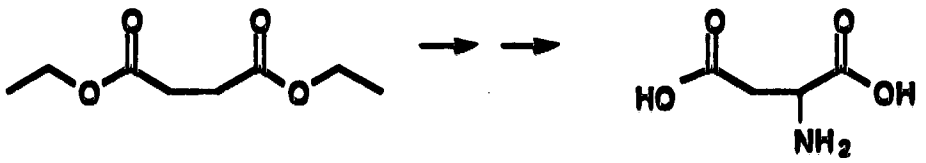
Scheme 10:



Initially it was essential to establish if reagent **18** is indeed capable of electrophilic amination of enolates. Ethyl phenylacetate (**19**) and diethyl succinate (**20**) were chosen as the starting materials for these studies, since they would lead to the amino acids phenylglycine (**21**) and aspartic acid (**22**) respectively, after cleavage of the protecting groups from the aminated product and reductive hydrogenolysis of the N-N bond.



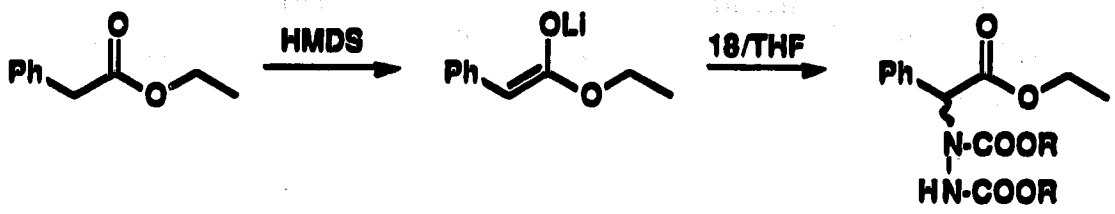
19 **21**



20 **22**

Treatment of **19** with lithium diisopropylamide (LDA) gives the enolate which reacts with dimenthyl azodicarboxylate (**18**) to produce a 22% yield of **23**. Since it is known[134] that certain anion oxidations function more efficiently with hexamethyldisilazide (HMDS) as the base, these conditions were attempted with **19**. In this case amination of **19** affords compound **23** as a 2:1 mixture of diastereomers in 59% yield (Scheme 11).

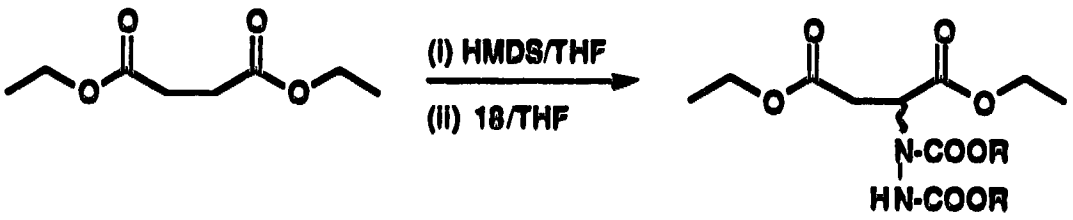
Scheme 11:



19 R = Menthyl 23

The diastereomeric ratio of **23** was determined from the relative integrations of the α-hydrogen in the high temperature (100 °C) ^{1}H NMR spectra. Formation of the enolate of **20** with HMDS as the base and amination with dimenthyl azodicarboxylate (**18**) at -78 °C produces a 1:1 mixture of diastereomers **24**, in 13% yield which is isolated after repeated chromatography (Scheme 12). Again the diastereomeric ratio was seen in the high temperature ^{1}H NMR spectra.

Scheme 12:

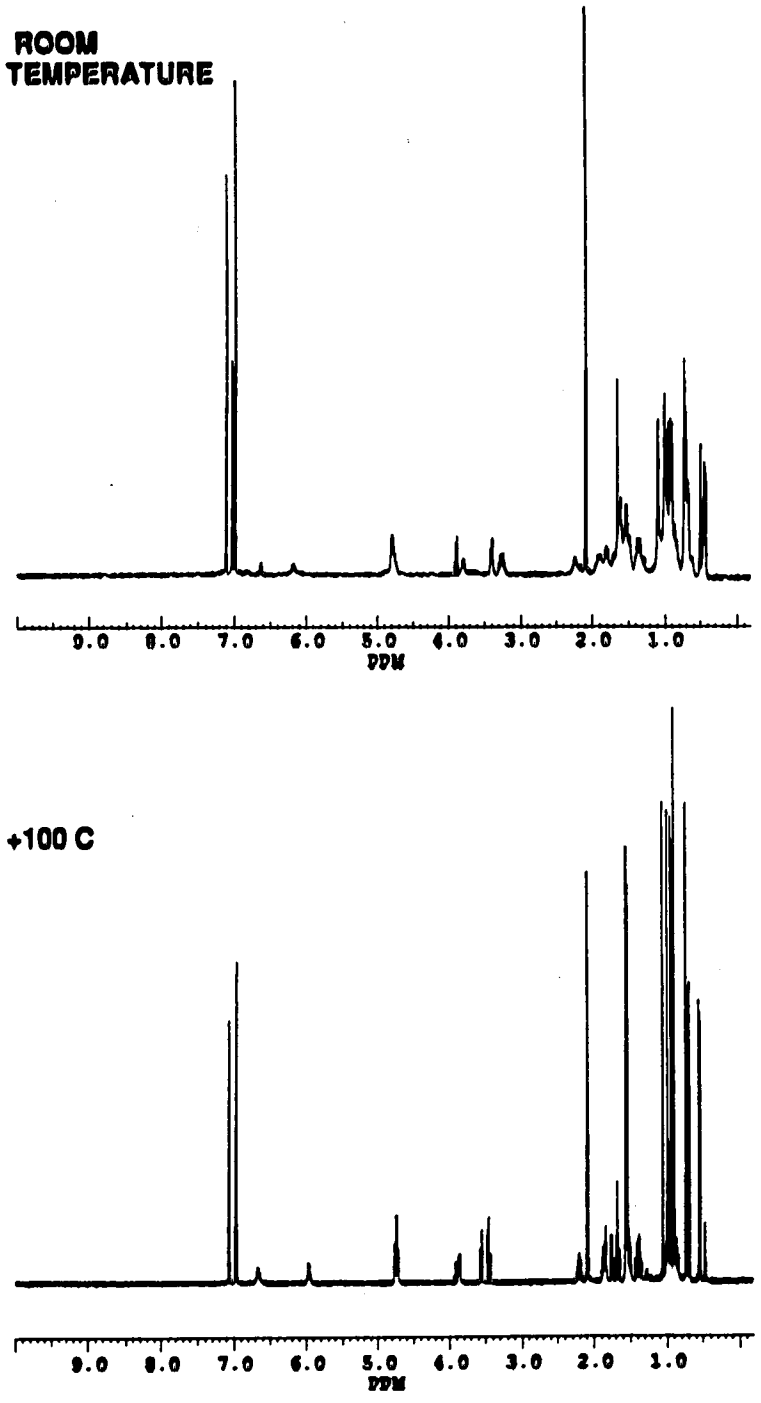


20 R = Menthyl 24

Previous studies on reaction of enolates with azodicarboxylates[99] have shown that the normal ^{1}H NMR spectra of the products display broad peaks at room temperature due to the rotational isomerism of the carbamate bonds. High temperature ^{1}H NMR spectra at 373

^{o}K in toluene d_8 affords sharp peaks because increase in temperature causes an increase in the rotational speed of the various isomers. Thus the signal observed is an average of the signals of the various isomers. (Figure 9).

Figure 9: Sample variable temperature ^{1}H NMR spectra 373 ^{o}K in toluene d_8 to show peak resolution



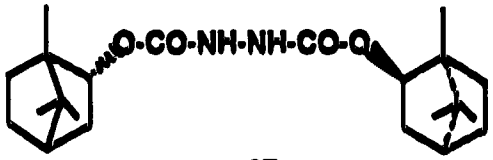
A critical future for the utility of this method for the production of α-hydrazino acids and α-amino acids is the ability to easily remove all protecting groups. This provides a method for determination of the absolute configuration of the newly created chiral center. Unfortunately, attempts to cleave the menthyl groups from **23** and **24** using hydrochloric acid (6N) or concentrated HI failed; only starting material was seen by thin layer chromatography.

Since the menthyl protecting groups could not be readily cleaved by acidic hydrolysis and previous experience[99] had shown that α-hydrazino acids are unstable in base, a different chiral substituent was necessary. Borneol (**25**) was chosen as the next chiral molecule for synthesis of an azodicarboxylate reagent, because cleavage of the borneol group could give the stable bornyl cation.[135] Reaction of borneol with phosgene by a procedure similar to that used with menthol gives the bornyl chloroformate (**26**). This was not isolated, but treated directly with half an equivalent of hydrazine at 20 °C to generate **27** in 55% yield. Oxidation of the hydrazo group in **27** with NBS affords dibornyl azodicarboxylate (**28**) in 77% yield (Scheme 13).

Amination of the enolate of ethyl phenylacetate (**19**) with **28** appears to lead to a single diastereomer **29** in 57% yield based on high temperature ^{1}H NMR spectra. However the similar reaction of the enolate of diethyl succinate (**20**) forms a 1:1 mixture of diastereomers **30** in 49% yield, which could be seen from two sets of resonances in the high temperature ^{1}H NMR spectra.

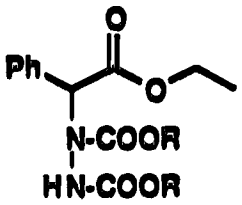
Scheme 13:

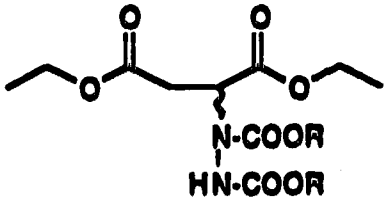
25 26



27

28



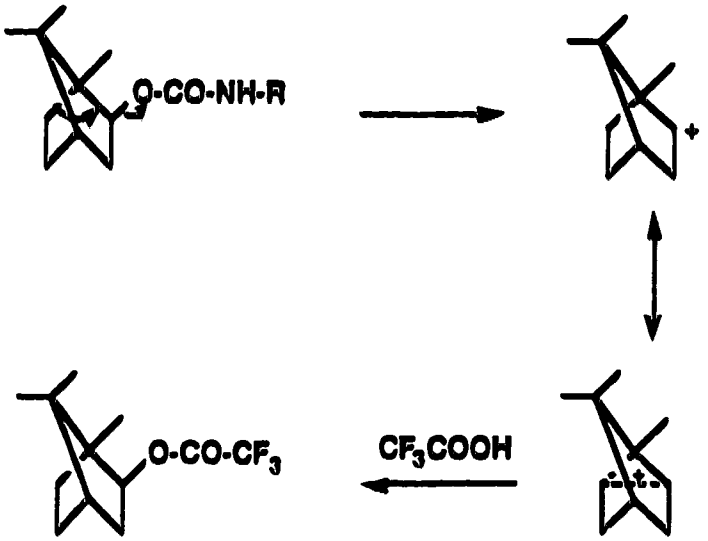


29 R = Bornyl 30

Unfortunately, as with the menthyl derivatives, cleavage of the bornyl groups with concentrated acids like HBr fails, and only starting material could be seen by thin layer chromatography. Hence conversion to the parent hydrazino acids and definitive confirmation of the stereochemical outcome of the amination reactions could not be completed.

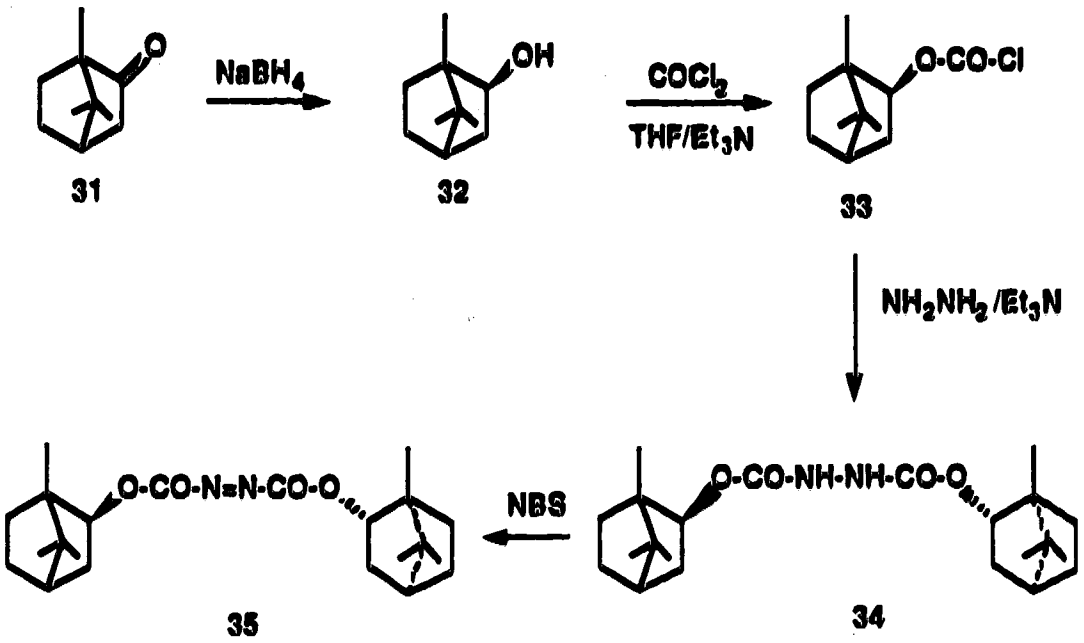
Studies by Fugino et al.[136,137] indicate that trifluoroacetic acid at room temperature rapidly cleaves the isobornyl esters, which as a result are useful as protecting groups in peptide synthesis. The facile removal of the isobornyl group relative to the bornyl group is due to the correct alignment of the bonds which allows direct anchimeric assistance in the cleavage process (Scheme 14).

Scheme 14:



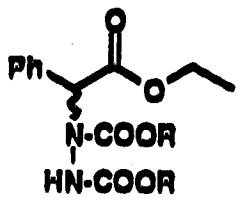
The easy removal of the isobornyl protecting group suggested use of isoborneol as a suitable chiral auxiliary. Since L-isoborneol (32) is not readily available, it was prepared by the sodium borohydride reduction of D-camphor (31) in 73% yield. The other product of the reaction is borneol, formed by the hydride attack from the more hindered side. Compound 32 could be transformed into the diisobornyl azodicarboxylate (35) by the usual procedure as outlined in Scheme 15. Reaction of 32 with phosgene proceeds in 80% yield. Condensation of two equivalents of isobornyl chloroformate (33) with one equivalent of hydrazine affords the diisobornyl hydrazodicarboxylate (34) in 55% yield. N-Bromosuccinimide oxidation of 34 produces the azodicarboxylate 35 in 91% yield.

Scheme 15:



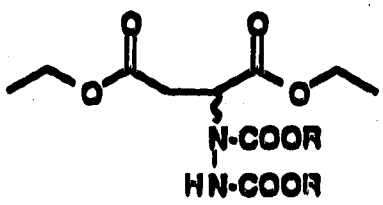
Amination of the achiral enolates of ethyl phenylacetate (19) and diethyl succinate (20) at -78 °C with 35 in each case leads to a 1:1 mixture of diastereomers.

Compounds **36** and **37** are produced in 42% and 41% yield, respectively. As before, the diastereomeric ratios were determined by high temperature ^{1}H NMR spectral analysis.



36

R = Isobornyl



37

In summary, the use of achiral enolates and a chiral dialkyl azodicarboxylates gives modest yields but leads generally to a 1:1 mixture of diastereomers with the exception of products **23** and **29**, as outlined in Table 1.

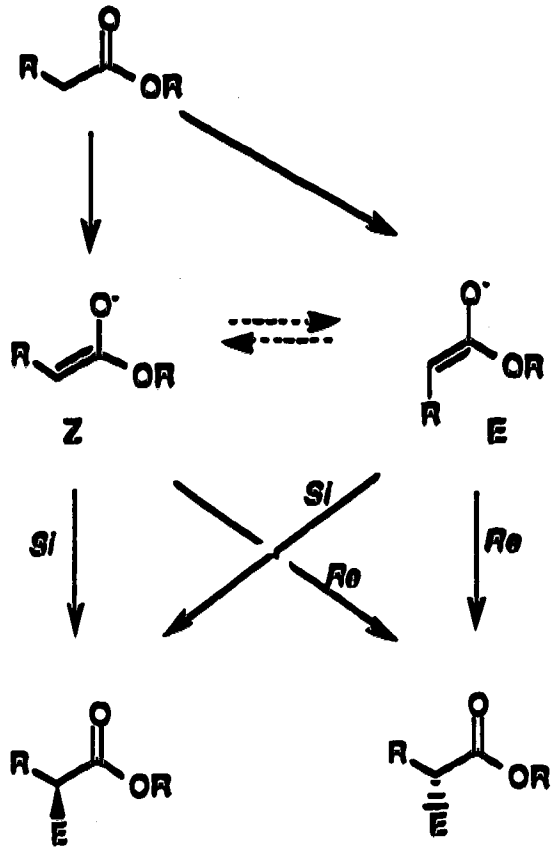
Table 1: Summary of aminations of achiral substrates with ROOC-N=N-COOR.

Reagent	Ethyl Phenylacetate			Diethyl Succinate		
R	Product	Yield%	Ratio[a]	Product	Yield%	Ratio[a]
Menthyl (**18**)	**23**	57	2:1	**24**	13	1:1
Bornyl (**28**)	**29**	57	1:0	**30**	49	1:1
Isobornyl (**35**)	**36**	41	1:1	**37**	41	1:1

[a] : ratio of diastereomers determined by high temperature ^{1}H NMR spectra.

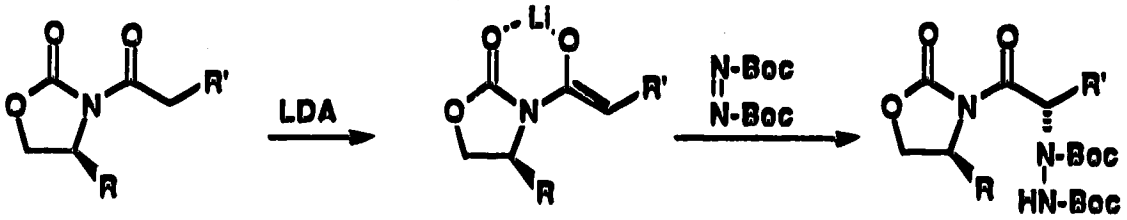
The formation of such diastereomeric mixtures could be due either to a lack of facial selectivity or to the existence of ester enolates in both the *E* and *Z* conformations[138], or due to a combination of both factors. If the chiral dialkyl azodicarboxylate is unable to distinguish between the two enolate isomers, attack from the same face of the enolate would produce different diastereomers (Figure 10). Hence we decided to examine both chiral ester enolates which have a single preferred geometry.

Figure 10: Conformations of enolates and direction of attack by the dialkyl azodicarboxylate



Studies in our research group[99] as well as by Evans et al.[51] of the reaction of enolates of chiral carboximides and achiral dialkyl azodicarboxylates indicate that the reaction occurs in a highly stereoselective manner to give predominantly one of two possible diastereomers. (Scheme 16)

Scheme 16:

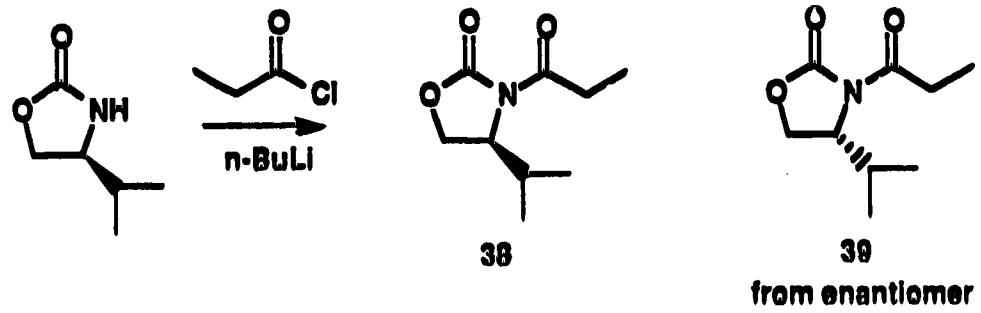


Preferential formation of the *Z* enolate[139] occurs because of the steric repulsion between the side chain R' and the R group of the oxazolidinone. It is believed that the enolate and the oxazolidinone oxygens chelate with the Li cation, thereby preventing rotation about the carbon-nitrogen bond and forming a rigid system. The bulky R group (isopropyl or benzyl) then directs the incoming electrophile from the opposite face (*si*). The aminated products are obtained in diastereomeric ratios ranging from 72:28 to > 99:1.[55,99] Unfortunately their separation is sometimes quite difficult.[99]

The work described above shows that with the possible one exception asymmetric induction with a chiral dialkyl azodicarboxylate reagent and achiral ester enolates is poor. However, if the enolate geometry is fixed in a single conformation, a potential source of loss of stereochemical purity would be eliminated. Futhermore, invoking the principle of double diastereodifferentiation,[140-142] it appeared that use of a chiral dialkyl azodicarboxylate reagent and a chiral substrate could alter the diastereomeric ratio in the products. The bulk of the isobornyl group could also potentially improve the

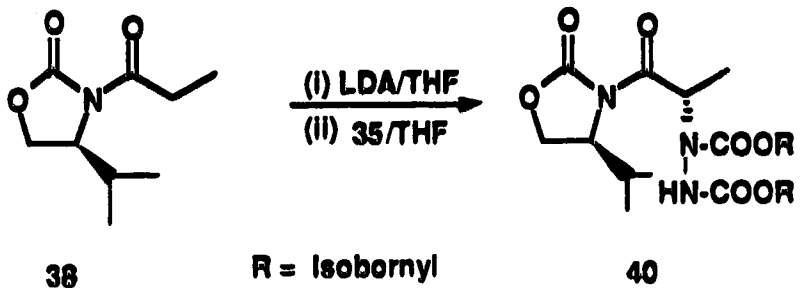
ratio with a chiral enolate. The carboximides used in this study can be prepared according to the procedure of Evans et al.[143,144] from readily available starting materials.[128] (Scheme 17)

Scheme 17:



The enolate of **38** was prepared in the normal way using LDA as the base[52] at -78 °C and then aminated with diisobornyl azodicarboxylate (**35**) to produce the compound **40** in 56% yield. (Scheme 18)

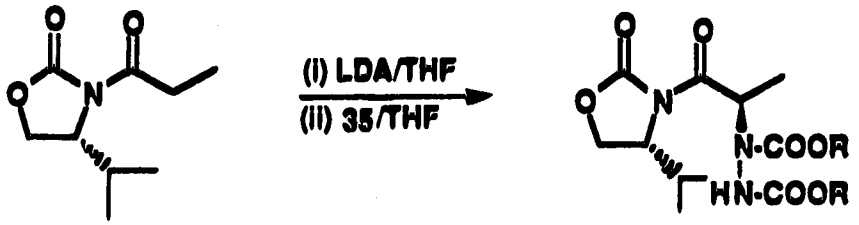
Scheme 18:



High temperature ^{1}H NMR spectra at 373 °K in toluene d_8 on the product **40** suggests that it is a single diastereomer. Amination of the other isomer **39**, formed under similair

conditions,with diisobornyl azodicarboxylate (**35**) also yields only one isomer **41** in 88% yield. (Scheme 19)

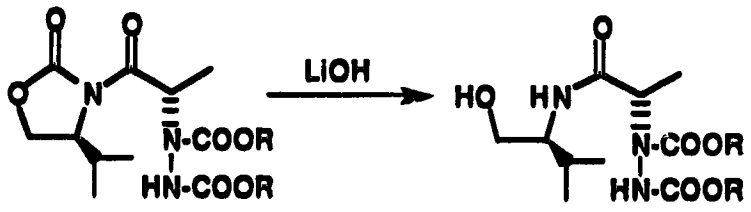
Scheme 19:



39 **R = Isobornyl** **41**

Since the ^1H NMR spectra of the two carboximides **40** and **41** are very similar, it appeared essential to remove the chiral auxiliary and to confirm the stereochemistry of the reactions. Cleavage of **40** and **41** with base (LiOH) poses problems in the isolation of the desired acid. The only product isolated after repeated preparative thin layer chromatographic separations was compound **III** which arises from hydroxide attack at the carbonyl carbon of the oxazolidinone moiety in the aminated product (Scheme 20).

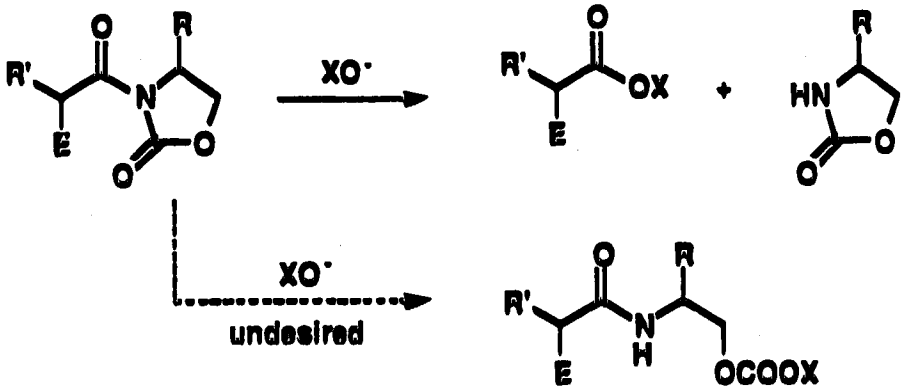
Scheme 20:



40 **R = Isobornyl** **III**

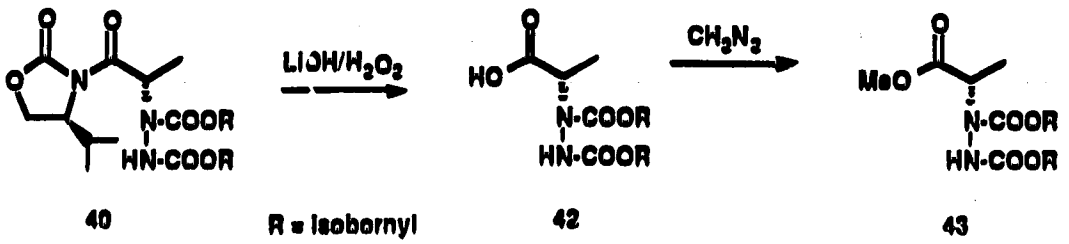
Recent studies by Evans et al.[145] indicate that hydroperoxide cleaves chiral carboximides cleanly to afford the desired acids without significant epimerisation or undesired oxazolidinone cleavage (Scheme 21).

Scheme 21:



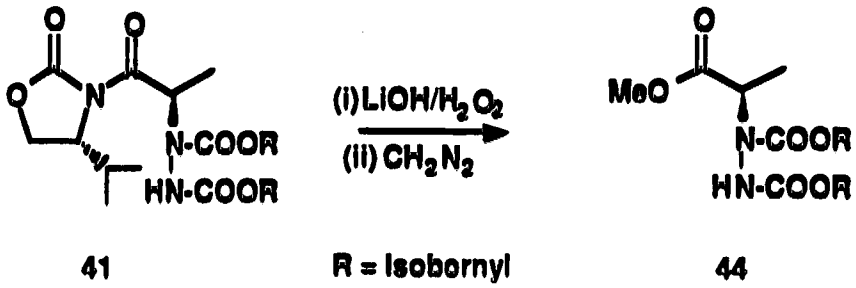
However the lipophilicity of the isobornyl in the product still causes problems in the isolation of the acid which was obtained using the hydroperoxide cleavage procedure[145] ($LiOH/H_2O_2$; 3:1 THF:H_2O 0 °C). Repeated purifications are necessary to obtain a small amount (27%) of the acid **42**. One of the main problems encountered in the isolation of the acid **42** is the similarity of its chromatographic behaviour to that of the oxazolidinone. Hence the direct conversion of the acid to its methyl ester **43** with freshly prepared diazomethane[146] allows facile separation and gives an 86% yield (Scheme 22).

Scheme 22:



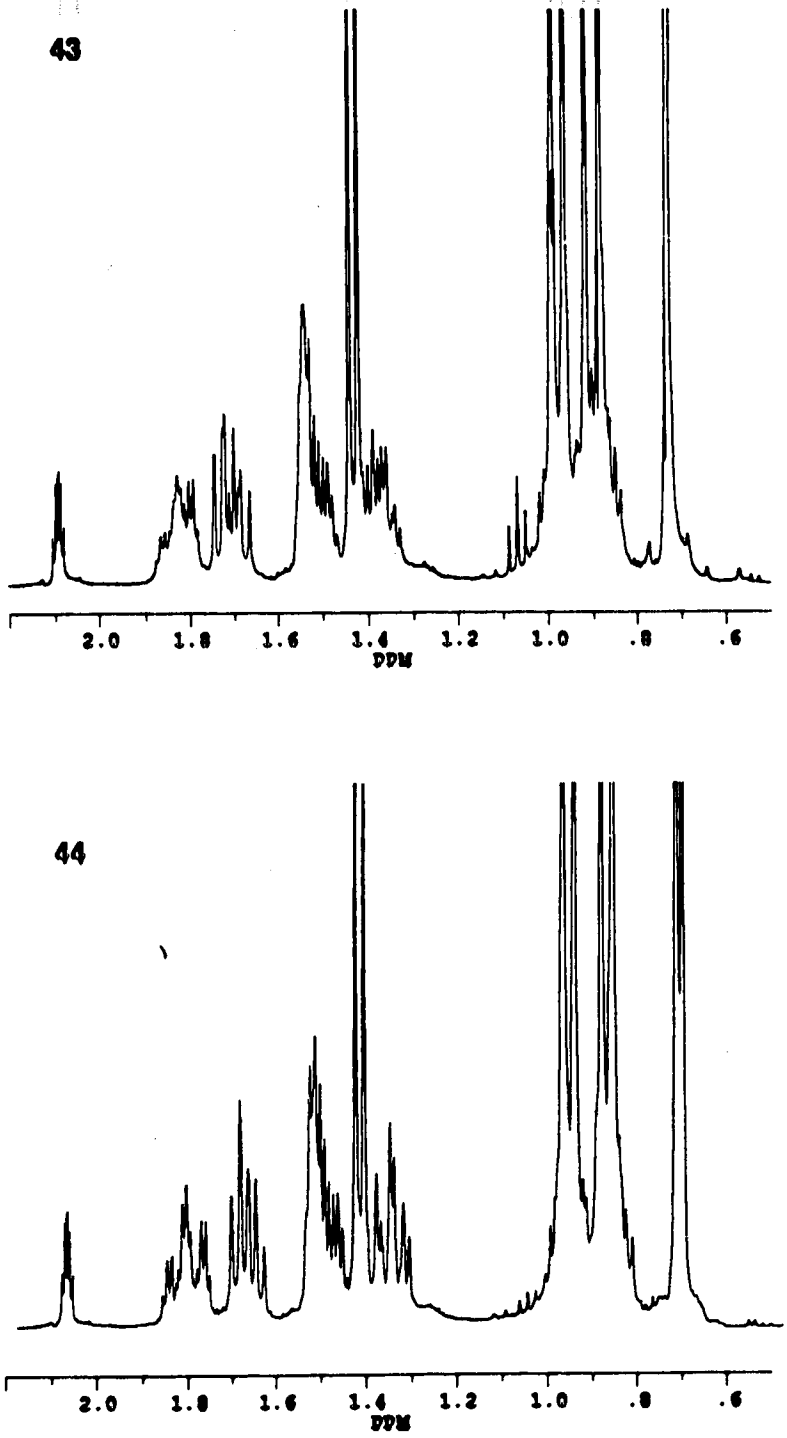
The $LiOH/H_2O_2$ procedure[145] also cleaves the aminated product **41**, which upon acidification with formic acid and reaction with diazomethane,[146] produces the methyl ester **44** in 87% yield (Scheme 23).

Scheme 23:



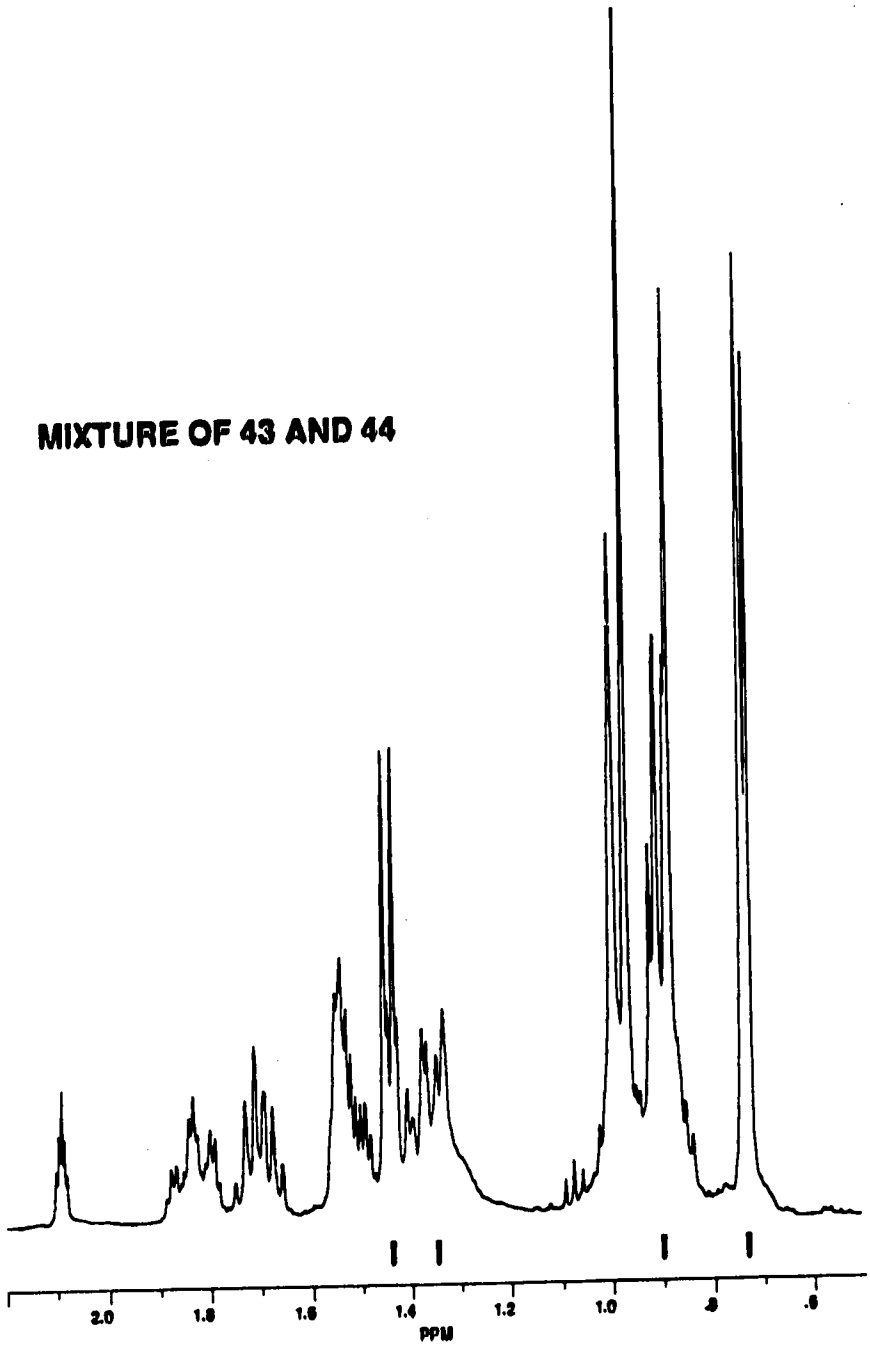
The high temperature (373 °K) ^1H NMR spectra of the two diastereomeric methyl esters **43** and **44** are clearly different as seen in Figure 11. Close examination of the spectra shows differences in the regions at δ 0.7, 0.9 1.35 ppm. In addition the doublet at δ ~ 1.4 ppm due to the α-methyl group has slightly different chemical shifts in the diastereomers **43** and **44**.

Figure 11: Comparision of the ^1H NMR spectra of 43 (top)and 44 (bottom).



These observations are confirmed by the examinations of analogous spectra of a 1:3.75 mixture of **43** and **44** (Figure 12). Each amination, hydrolysis, esterification sequence

Figure 12: Mixture ^{1}H NMR spectra of 43 and 44 in toluene d_8 at +100 °C.

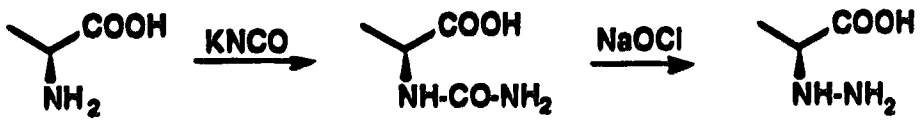


gives either pure **43** or pure **44**, and the chromatographic properties of the intermediates in each series are identical. Hence we can conclude that the individual aminations proceed with nearly complete diastereoselection. This result is in contrast to the diastereomer ratio of 90:10 obtained by Trimble[99] in the amination of **38** and **39** with achiral dibenzyl azodicarboxylate, under similar conditions.

Since each of the oxazolidinone enolate enantiomers reacts with the same enantiomer of diisobornyl azodicarboxylate (**35**) with nearly complete diastereoselection, no double diastereodifferentiation effects are observed. A similair result was shown by Evans et al.[147] in an aldol reaction wherein the use of enantiomeric aldehydes with a single oxazolidinone enolate gave only one product. The chiral centre in the enolate controlled the stereochemistry of the newly created center.

The identity and absolute configuration of the products could be confirmed by an independent synthesis[148] of one of the methyl ester isomers. Reaction of L-alanine (**45**) with potassium cyanate[149] converts the former to ureidopropionic acid (**46**). This then undergoes a Hofmann rearrangement [68] to yield hydrazinopropionic acid (**47**) (Scheme 24).

Scheme 24:



45 **46** **47**

Reaction of **47** with isobornyl chloroformate[136,150] **(33)** affords a crude acid which is methylated directly with a freshly prepared ether solution of diazomethane[146] to produce the methyl ester **48** (Scheme 25). Its spectral data and chromatographic properties correspond exactly to those of the methyl ester **43** obtained from the amination product **40**. The summary of the amination studies with **35** on the oxazolidinones is listed in Table 2.

Scheme 25:

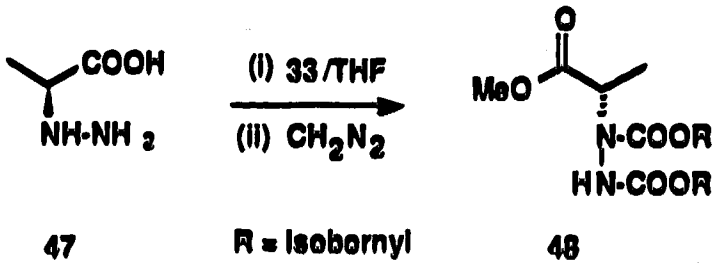


Table 2: Summary of the amination studies on the oxazolidinones with **35**

Oxazolidinone	Product on Amination		Product on Cleavage and Methylation	
	Compound	Yield%	Compound	Yield%
38	**40**	56	**43**	86
39	**41**	88	**44**	87

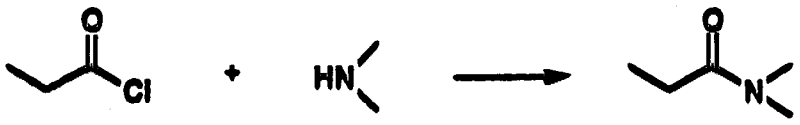
Since the stereochemistry of amination of chiral carboximide enolates is controlled by the oxazolidinone, we decided to investigate the amination of achiral enolates of disubstituted amides wherein the substituent on the nitrogen forces preference for one conformation, namely *Z*. [138,151-156] Hence reaction with a chiral aminating reagent may give predominance of one diastereomer if face selectivity can be controlled by the isobornyl substituents (Figure 13).

Figure 13: Conformation of amide enolates

1 Z

The required amide was prepared by reaction of excess dimethyl amine and propionyl chloride at 0 °C to yield N,N-dimethylpropionamide (**49**) in 87% yield (Scheme 26).

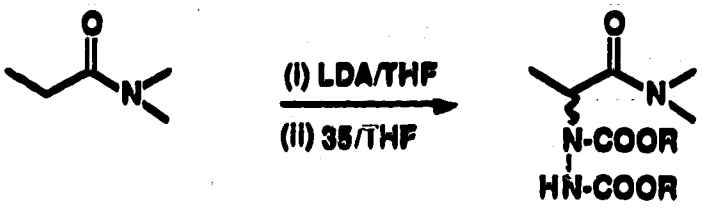
Scheme 26:



49

Unfortunately, formation of the enolate of **49** with LDA at -78 °C, followed by amination[52] with diisobornyl azodicarboxylate (**35**) gave **50** as 1:1 mixture of diastereomers in 72% yield (Scheme 27). As before, the ratio was determined by the high temperature ^{1}H NMR spectra.

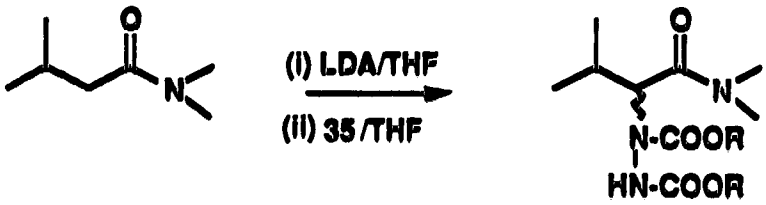
Scheme 27:



49 R = Isobornyl 50

In order to test whether additional steric hindrance in the alkyl side chain affects the diastereomeric ratio, N,N-dimethylisovaleramide (**51**) was prepared in 76% yield by a procedure analogous to that used to prepare **49**. Formation of the enolate and amination[52] at -78 °C with diisobornyl azodicarboxylate produces **52** in 87% yield as a 1:1 mixture of diastereomers analyzed by the high temperature ^{1}H NMR spectrometry (Scheme 28).

Scheme 28:



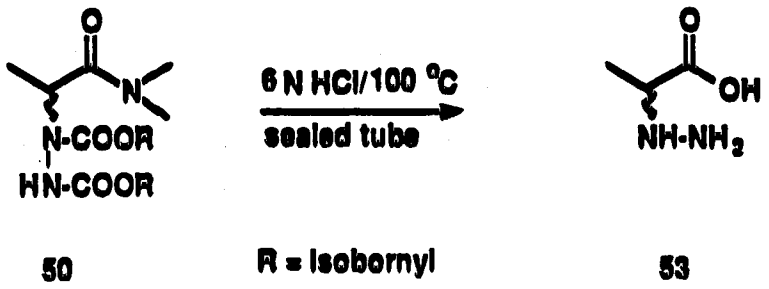
51 R = Isobornyl 52

Apparently the chiral isobornyl substituents have little influence on the amination of the achiral amide enolates regardless of the size of the alkyl chain.

The free hydrazino acids can be obtained by heating the compound in a sealed tube with hydrochloric acid (6N).[157] Hence, such treatment of **50** produces racemic

hydrazinopropionic acid (53) in 75% yield after purification by cation exchange chromatography (Scheme 29).

Scheme 29:



50 R = Isobornyl 53

In summary, a series of chiral dialkyl azodicarboxylates were synthesized and their reactions with various achiral ester and amide enolates and chiral carboximide enolates were examined as a potential route to α-hydrazino acids and α-amino acids. Although formation of an intramolecular azodicarboxylate bridge between the hydroxyls of N,N-diethyl chenodeoxycholamide or N,N-diethyldexoycholamide could not be achieved, readily available monoterpene alcohols such as menthol, borneol, and isoborneol can be converted to the corresponding azodicarboxylate esters. Aminations of ester enolates proceed well, but with possibly one exception (ethyl phenylacetate) do not give significant asymmetric induction at the newly created chiral center. Furthermore, only the derivatives bearing isobornyl groups can be readily cleaved to the parent α-hydrazino acids. Studies with enolates of chiral carboximides ("Evans enolates") show greatly improved diastereo-selection as compared with simple achiral dialkyl azodicarboxylates, however the stereochemical control is exercised by the oxazolidinone moiety alone and no effects of double diastereodifferentiation can be seen. Apparently, the extra steric demand of the

bulky isobornyl group accounts for the improvement. Simple achiral enolates of N,N-dimethyl amides possess a defined enolate geometry (in contrast to ester enolates), but unfortunately do not display significant asymmetric induction in their reaction with diisobornyl azodicarboxylate.

EXPERIMENTALS

General

All reactions were done under a positive pressure of dry Ar; those requiring non aqueous conditions were performed using oven dried glassware which was cooled under Ar. Dry solvents were prepared under an Ar atmosphere according to Perrin *et al.*[130] All solvents were distilled before use. All organic layers obtained from extractions were dried over anhydrous Na_2SO_4. The term "*in vacuo*" refers to removal of solvent on a rotary evaporator followed by evacuation (< 0.05 mm Hg) to a constant sample weight. All reactions were monitored by TLC using either UV absorption, I_2 staining, ninhydrin (amino acids), bromocresol green (acids), or p-dimethylaminobenzaldehyde (hydrazino acids) spray for visualization. Commercial thin layer chromatography (TLC) plates were silica, Merck 60F-254, or Merck RP-$8F_{254}S$. Silica gel for column chromatography was Merck type 60, 70 - 230 mesh. Flash chromatography employed by the method of Still *et al*[158] with Merck type 60 silica gel, 230 - 420 mesh. Normal phase medium pressure liquid chromatography (MPLC) was done using Merck type 60H silica gel.

Melting points were determined either on a Thomas Hoover or Buchi apparatus using open end capillary tubes and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker WP - 80, WH - 200, AM - 300, WM - 360, or WH - 400 instruments in the specified deuterated solvent with tetramethylsilane (TMS) as the internal standard. Infrared spectra (IR) were determined with a Nicolet 7199 FT-IR spectrometer. Mass spectra (MS) were recorded with an ionising voltage of 70eV on an AEI MS-50 instrument for electron impact (EI) ionisation, on a MS-12 for chemical ionisation (CI) and on a MS-9 for fast atom bombardment (FAB). All literature compounds had ^1H NMR, IR and MS spectra consistent with assigned structures. Optical rotations were measured on Perkin-Elmer 241 or 141 polarimeters with a micro cell (100 mm, 0.9 mL) or a standard cell (100 mm, 8 ml) respectively .

N,N-Diethylchenodeoxycholamide (3)

The compound was prepared by a modification of the procedure of Bellini and coworkers.[120] To chenodeoxycholic acid (3.93 g, 10.0 mmol) in 50 mL dioxane at 10 °C was added triethylamine (1.39 mL, 10.0 mmol), followed by ethyl chloroformate (0.956 mL, 10.0 mmol), and the mixture was stirred at 10 °C for 10 min. Diethylamine (2.59 mL, 25.0 mmol) was added and the mixture was stirred for 15 min at 10 °C and then at 20 °C for 2 h. The mixture was poured into 50 mL $KHCO_3$, extracted (3 x 60 mL) with EtOAc. The organic phases were combined, dried, and concentrated *in vacuo* to yield 5.90 g of a white viscous substance which was purified by normal SiO_2 (3 cm wide) column chromatography to yield 4.05 g (90% yield) of a white solid **3**: mp 166 - 170 °C; IR ($CHCl_3$ cast) 3420, 2920, 1626, 1448, 1380 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.86 (m, 1H, 7-C<u>H</u>), 3.46 (m, 1H, 3-C<u>H</u>), 3.40-3.26 (m, 4H, N(C<u>H</u>$_2$-)$_2$), 2.34 (m, 1H, C<u>H</u>HCO), 2.24 (m, 1H, CH<u>H</u>CO), 2.17 (m, 1H), 2.08 - 1.47 (m, 17H), 1.46 - 1.24 (m, 8H), 1.20 (t, 7.0 Hz, 3H, NCH$_2$C<u>H</u>$_3$), 1.12 (t, 7.0 Hz, 3H, NCH$_2$C<u>H</u>$_3$) 0.97 (d, 6.5 Hz, 3H, 21-C<u>H</u>$_3$), 0.92 (s, 3H, 19-C<u>H</u>$_3$), 0.67 (s, 3H, 18-C<u>H</u>$_3$); exact mass 447.3711, (calcd for $C_{28}H_{49}NO_3$ 447.3713). Anal. Calcd for $C_{28}H_{49}NO_3$: C, 75.12; H, 11.03; N, 3.13.Found: C, 75.27; H, 10.96; N, 3.05.

N,N-Diethyldeoxycholamide (4)

The compound was prepared by a modification of the procedure of Bellini and coworkers.[120] To deoxycholic acid (3.93 g, 10.0 mmol) in 50 mL dioxane at 10 °C, was added n-tributylamine (2.38 mL, 10.0 mmol) followed by ethyl chloroformate (0.956 mL, 10.0 mmol) and the mixture was stirred at 10 °C for 10 min. Diethylamine (2.59 mL, 25.0 mmol) was added, and the mixture stirred for 15 min at 10 °C and then at 20 °C for 2 h. The mixture was poured into cold water, extracted (3 x 40 mL) with EtOAc. The organic phases were combined, dried and concentrated *in vacuo* to yield 6.39 g of a white viscous substance.The compound was purified on a normal SiO_2 (3 cm wide) column to yield 3.75

g (84% yield) of a white solid **4**: mp 168 - 170 °C; IR ($CHCl_3$ cast) 3400, 2938, 1626, 1463, 1448, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (t, 2.5 Hz, 1H, 12-C<u>H</u>), 3.62 (m, 1H, 3-C<u>H</u>), 3.43 - 3.25 (m, 4H, N($C\underline{H}_2$-)$_2$), 2.35 (m, 1H, C<u>H</u>HCO), 2.21 (m, 1H, CH<u>H</u>CO), 1.94 - 1.47 (m, 18H), 1.46 - 1.36 (m, 6H), 1.34 - 1.22 (m, 2H), 1.17 (t, 7.0 Hz, 3H, $NCH_2C\underline{H}_3$), 1.10 (t, 7.0 Hz, 3H, $NCH_2C\underline{H}_3$), 0.99 (d, 6.5 Hz, 3H, 21-$C\underline{H}_3$), 0.91 (s, 3H, 19-$C\underline{H}_3$), 0.68 (s, 3H, 18-$C\underline{H}_3$); exact mass 447.3719, (447.3712 calcd for $C_{28}H_{49}NO_3$). Anal. Calcd for $C_{28}H_{49}NO_3$: C, 75.12; H, 11.03; N, 3.13. Found: C, 75.17; H, 10.93; N, 3.07.

Reaction of succinyl chloride with N,N-diethylchenodeoxycholamide

The amide **3** (2.24 g, 5.00 mmol) was dissolved in $CHCl_3$ (20 mL) and cooled to 0 °C. Pyridine (0.607 mL, 7.50 mmol), and succinyl chloride (0.551 mL, 5.00 mmol) were added and the mixture stirred at 0 °C for 30 min and then at 20 °C for 24 h.Water (2 mL) was added and extracted (3 x 15 mL) with $CHCl_3$. Organic phases combined, washed with $NaHCO_3$ (15 mL), dried, and concentrated *in vacuo* to yield 3.45 g of a black viscous substance. This was purified by normal SiO_2 (3 cm wide) column chromatography to yield 2.26 g (82% yield) of a pale yellow substance **5**: IR ($CHCl_3$ cast) 3440, 2940, 1730, 1630, 1460, 1380, 1270, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (m, 1H), 3.85 (bs, 1H), 3.33 (m, 4H), 2.56 (s, 2H), 2.33 (m, 2H), 2.18 (m, 1H), 1.91 (m, 8H), 1.66 (m, 4H), 1.39 (m, 13H), 1.18 (t, 7.0 Hz, 3H), 1.11 (t, 7.0 Hz, 3H), 0.95 (d, 7.0 Hz, 3H), 0.91 (s, 3H), 0.56 (s, 3H); FAB MS 548.54 (MH^+).

Reaction of adiopyl chloride with N,N-diethylchenodeoxycholamide

The amide **3** (0.224 g, 0.500 mmol) was dissolved in $CHCl_3$ (5 mL) and cooled to 0 °C. Pyridine (0.081 mL, 1.00 mmol), and adipoyl chloride (0.073 mL, 0.500 mmol) were added and the reaction stirred at 0 °C for 30 min and then at 20 °C for 24 h. Water (2 mL) added and the mixture was extracted (3 x 5 mL) with $CHCl_3$. Organic phases

combined,washed with $NaHCO_3$ (5 mL), dried, and concentrated *in vacuo* to yield 0.394 g of a white viscous substance which was purified by normal SiO_2 (3 cm wide) column chromatography, followed by flash chromatography (95:5 $CHCl_3$:MeOH) to yield 0.076 g (26% yield) of a colorless substance **6**: IR ($CHCl_3$ cast) 3440, 2932, 2838, 1728, 1627, 1463, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (m, 1H), 3.87 (bs, 1H), 3.35 (m, 4H), 2.26 (m, 8H), 2.00 (m, 3H), 1.81 (m, 8H), 1.65 (m, 7H), 1.39 (m, 11H), 1.18 (t, 7.0 Hz, 3H), 1.11 (t, 7.0 Hz, 3H), 0.95 (d, 6.0 Hz, 3H), 0.92 (s, 3H), 0.66 (s, 3H); FAB MS 430.51 (M^+-$C_6H_{10}O_4$).

Reaction of glutaryl chloride with N,N-diethylchenodeoxycholamide

The amide **3** (1.72 g, 3.85 mmol) was dissolved in $CHCl_3$ (20 mL) and cooled to 0 °C. Pyridine (0.623 mL, 7.70 mmol), and glutaryl chloride (0.491 mL, 3.85 mmol) were added and the mixture stirred at 0 °C for 30 min, then at 20 °C for 24 h, and heated to 55 °C for 4 h. The reaction was cooled, water (2 mL) added, and then extracted (3 x 15 mL) with $CHCl_3$. The organic phases were combined, washed with $NaHCO_3$, dried, and concentrated *in vacuo* to yield 1.99 g of an orange solid which was purified by flash chromatography (97:3 CH_2Cl_2:MeOH) to yield 1.38 g (66% yield) of a white fluffy solid **7**: IR ($CHCl_3$ cast) 2940, 2865, 1731, 1640, 1450, 1250, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.60 (m, 1H), 3.34 (m, 4H), 2.49 (m, 1H), 2.34 (m, 3H), 2.15 (m, 2H), 1.87 (m, 9H), 1.43 (m, 16H), 1.18 (t, 7.0 Hz, 3H), 1.10 (t, 7.0 Hz, 3H), 0.95 (d, 6.0 Hz, 3H), 0.92 (s, 3H), 0.65 (s, 3H); MS (CI-NH_3) *m/z* 544.5223 (MH^+).

Reaction of succinyl chloride with N,N-diethyldeoxycholamide

The amide **4** (1.52 g, 3.39 mmol) was dissolved in $CHCl_3$ (20 mL) and cooled to 0 °C. Pyridine (0.548 mL, 6.78 mmol) and succinyl chloride (0.373 mL, 3.39 mmol) were added and the mixture stirred at 0 °C for 30 min, then at 20 °C for 24 h,and heated to 55 °C for 4 h. Mixture was cooled, H_2O (2 mL) added, extracted (3 x 15 mL) with $CHCl_3$.

The organic phases were combined, washed with $NaHCO_3$, dried, and concentrated *in vacuo* to yield 1.64 g of an black solid. This was purified by normal SiO_2 (4 cm wide) column chromatography to yield 0.819 g (46% yield) of a colorless substance **8**: IR ($CHCl_3$ cast) 2940, 1733, 1640, 1445, 1260, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 1H), 4.78 (s, 1H), 3.35 (m, 4H), 2.64 (m, 3H), 2.35 (m, 1H), 2.18 (m, 1H), 1.86 (m, 4H), 1.64 (m, 9H), 1.45 (m, 9H), 1.45 (m, 5H), 1.30 (m, 7H), 1.70 (t, 7.0 Hz, 3H), 1.10 (t, 7.0 Hz, 3H), 0.92 (s, 3H), 0.87 (d, 6.0 Hz, 3H), 0.74 (s, 3H); exact mass 530.3822 (530.3845 calcd for $C_{32}H_{52}NO_5$).

Bis phenyl carbonate of N,N-diethylchenodeoxycholamide (9)

The compound was prepared by a modification of the procedures of Feiser and coworkers[125] and Hansen and coworkers.[126,127] The amide **3** (1.50 g, 3.35 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. Pyridine (2.18 mL, 26.8 mmol), and phenyl chloroformate (2.52 mL, 20.1 mmol) were added and the reaction mixture was stirred at 20 °C for 24 h. Water (8 mL), and conc HCl (0.4 mL) were added and the mixture was stirred and heated on a steam bath for 20 min. This was cooled and extracted (3 x 15 mL) with Et_2O. The organic layers were combined, dried, and concentrated *in vacuo* to yield 4.39 g of a pale yellow substance.This was purified by flash chromatography (95:5 $CHCl_3$:MeOH) to yield 2.31 g (99% yield) of a white solid **9**: mp 122 - 125 °C; IR ($CHCl_3$ cast) 2939, 1841, 1757, 1409, 1266, 1251, 1181, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 -7.16 (m, 10H), 4.83 (b, 1H), 4.56 (m, 1H), 3.46 - 3.25 (m, 4H), 2.33 (m, 1H), 2.20 (m, 2H), 2.08 - 1.74 (m, 10H), 1.69 - 1.29 (m, 10H), 1.25 (m, 2H), 1.18 (t, 7.0 Hz, 3H), 1.10 (t, 7.0 Hz, 3H), 0.96 (d, 6.5 Hz, 3H), 0.94 (s, 3H), 0.67 (s, 3H); FAB MS 688.60 (MH^+). Anal. Calcd for $C_{42}H_{57}NO_7$: C, 73.32; H, 8.36; N, 2.04. Found C, 73.20; H, 8.14; N, 2.09.

Bis phenyl carbonate of N,N-diethyldeoxycholamide (10)

The compound was prepared by a modification of the procedure of Feiser and coworkers[125] and Hansen and coworkers.[126,127] The amide **4** (0.224 g, 0.500 mmol) was dissolved in dry THF (3 mL) and cooled to 0 °C. Pyridine (0.32 mL, 4.13 mmol), and phenylchloroformate (0.40 mL, 3.00 mmol) was added dropwise and the reaction stirred at 20 °C for 24 h. Water (4 mL), conc. HCl (0.10 mL) were added and the mixture stirred and heated on a steam bath for 20 min. This was cooled, extracted (3 x 5 mL) with Et_2O. Organic layers were combined, dried, concentrated *in vacuo* to yield 0.608 g of a pale white substance.This was purified by flash chromatography (99:1 CH_2Cl_2:MeOH) to yield 0.258 g (75% yield) of a white solid **10**: mp 59 - 62 °C; IR ($CHCl_3$ cast) 2295, 1757, 1630 , 1450, 1210, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.14 (m, 10H), 5.06 (bs, 1H, 12-C<u>H</u>), 4.76 - 4.66 (m, 1H, 3-C<u>H</u>), 3.46 - 3.26 (m, 4H), 2.39 (m, 1H), 2.23 (m, 1H), 2.03 - 1.77 (m, 10H), 1.65 - 1.31 (m, 14H), 1.18 (t, 7.0 Hz, 3H), 1.12 (t, 7.0 Hz, 3H), 0.99 (d, 6.5 Hz, 3H), 0.94 (s, 3H), 0.78 (s, 3H); FAB MS 688.81(MH^+). Anal. Calcd for $C_{42}H_{57}NO_7$: C, 73.33; H, 8.35; N, 2.04. Found: C, 73.45; H, 8.32; N, 1.94.

Reaction of hydrazine with bis phenyl carbonate of N,N-diethyl chenodeoxycholamide

To compound **9** (0.084 g, 0.12 mmol) dissolved in dry DMF (4 mL), was added triethylamine (0.033 mL, 0.24 mmol). Hydrazine hydrate (5.71 μL, 0.18 mmol) and DMAP (1 crystal) was added and the mixture stirred at 20 °C for 2 h. Quenched with H_2O (4 mL), when a white solution appeared. This was extracted (3 x 5 mL) with CH_2Cl_2. Organic phases combined, dried, and concentrated *in vacuo* to yield 0.082 g of a yellow oil,which was purified by flash chromatography (95:5 $CHCl_3$:MeOH) to yield 0.069 g of **11** (92% yield): IR ($CHCl_3$ cast) 3300, 2930, 1754, 1620, 1490, 1259, 1208, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 5H), 5.98 (s, 1H), 4.82 (s, 1H), 4.55 (m, 1H),

3.79 (bs, 2H), 3.36 (m, 4H), 2.36 (m, 1H), 2.21 (m, 1H), 2.14 - 1.66 (m, 11H), 1.66 - 1.25 (m, 10H), 1.19 (t, 7.0 Hz, 3H), 1.12 (t, 7.0 Hz, 3H), 0.95 (d, 6.5 Hz, 3H), 0.94 (s, 3H), 0.66 (s, 3H); FAB MS 626.37 (MH^+).

Reaction of hydrazine with bis phenyl carbonate of N,N-diethyl deoxycholamide

To compound **10** (0.120 g, 0.170 mmol) dissolved in dry DMF (5 mL), was added triethylamine (0.047 mL, 0.340 mmol). Hydrazine hydrate (8.2 µl, 0.260 mmol) and DMAP (0.27 µg) was added and the mixture stirred at 20 °C for 2 h, and heated to 60 °C for 30 min The reaction was quenched with H_2O (2 mL), and extracted (3 x 5 mL) with CH_2Cl_2. Organic phases combined, dried, and concentrated *in vacuo* to yield 0.161 g of a white oil. The mixture was purified by flash chromatography (90:10 Hexane:EtOAc) to yield 0.076 g (71% yield) of **12**: IR (CH_2Cl_2 cast) 3300, 2934, 1737, 1717, 1635, 1456, 1258, 1210, 1191 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 - 7.10 (m, 5H), 6.00 (s, 1H), 5.06 (s, 1H), 4.67 (m, 1H), 3.74 (bs, 2H), 3.35 (m, 4H), 2.34 (m, 1H), 2.19 (m, 1H), 2.11 - 1.68 (m, 11H), 1.68 - 1.22 (m, 13H), 1.17 (t, 7.0 Hz, 3H), 1.10 (t, 7.0 Hz, 3H), 0.94 (d, 6.5 Hz, 3H), 0.92 (s, 3H), 0.76 (s, 3H); exact mass 625.52 (MH^+) (625.85 calcd for $C_{36}H_{55}N_3O_6$).

Phenyl menthyl carbonate (14)

To the menthol (**13**) (4.69 g, 30.0 mmol) dissolved in dry THF (30 mL), and cooled to 0 °C, was added pyridine (4.85 mL, 60.0 mmol) and the mixture was stirred for 15 min. Phenyl chloroformate (7.53 mL, 60.0 mmol) was added when a white precipitate separated. Allowed to stir at 20 °C for 5.5 h. Water (30 mL) and conc HCl (1.5 mL) were added and the mixture was heated on a steam bath for 20 min. The mixture was allowed to cool, and extracted (3 x 25 mL) with Et_2O. Organic layers were combined, dried and concentrated *in vacuo* to yield 6.78 g of a colorless liquid which was purified by flash

chromatography (98:2 $CHCl_3$:MeOH) to yield 6.61 g (80% yield) of a colorless liquid **14**: IR ($CHCl_3$ cast) 2956, 2928, 2860, 1758, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 - 7.14 (m, 5H); 4.70 - 4.56 (dt, 1H); 2.17 (m, 1H); 2.06 (m, 1H); 1.76 - 1.64 (m, 2H); 1.57 - 1.42 (m, 2H); 1.16 (m, 2H); 0.98 - 0.80 (3d, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.32, 151.29, 129.55, 129.37, 125.78, 121.05, 120.90, 79.43, 47.07, 40.68, 34.09, 31.43, 26.27, 23.44, 21.97, 20.71, 16.38; MS (CI-NH_3) *m/z* 294.0171 (MNH_4^+). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.06; H, 8.80.

Menthyl carbazate (15)

To pyridine (2.07 mL, 26.0 mmol) in THF (30 mL) at 0 °C, was added hydrazine hydrate (1.09 mL, 34.0 mmol) followed by **14** (6.43 g, 23.0 mmol). The mixture was stirred at 0 °C for 60 min and then at 20 °C for 48 h. Water (22 mL) and conc HCl (2 mL) were added, and the mixture was extracted (3 x 25 mL) with $CHCl_3$. Organic phases were combined, dried, and concentrated *in vacuo* to yield 6.22 g of a solid which was purified to yield 4.15 g (84% yield) of a white solid **15**: mp 88 - 90 °C; IR ($CHCl_3$ cast) 3380, 2955, 2865, 1689, 1632, 1497, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (bs, 1H, NH), 4.59 (dt, 4.6, 10.5 Hz, 1H, CHO), 3.64 (bs, 2H, NH_2), 2.04 (m, 1H), 1.90 (m, 1H), 1.68 (m, 2H), 1.50 (m, 1H), 1.32 (m, 1H), 1.10 (m, 1H), 1.01 (m, 2H), 0.91 (d, 6.5 Hz, 3H), 0.89 (d, 7.0 Hz, 3H), 0.79 (d, 7.0 Hz, 3H); exact mass 214.1682 (214.1682 mass calcd for $C_{11}H_{22}N_2O_2$). Anal. Calcd for $C_{11}H_{22}N_2O_2$: C, 61.63; H, 10.35; N, 13.08. Found: C, 61.62; H, 9.94; N, 13.06.

Menthyl chloroformate (16)

This compound was prepared according to the procedure of Newman and coworkers.[129] Phosgene (15.2 mL, 220 mmol, d 1.432) was added via a cannula to menthol (31.2 g, 200 mmol) in dry THF (75 mL) at 20 °C, and the mixture was stirred for 45 minutes. Triethylamine (31.7 mL, 220 mmol) was added dropwise and a white

precipitate formed. The mixture was allowed to stir overnight at 20 °C. The solid was filtered and the filtrate was concentrated to yield 41.3 g (95% yield) of an orange liquid **16**: IR ($CHCl_3$ cast) 2960, 1775, 1460, 1170, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (dt, 4.0, 10.0 Hz, 1H, 3-C<u>H</u>), 2.14 (m, 1H, 8-C<u>H</u>), 1.95 (m, 1H, 2β-C<u>H</u>), 1.76 - 1.64 (m, 2H, 5α,6β-C<u>H</u>), 1.58 - 1.39 (m, 2H), 1.22 - 0.84 (m, 9H), 0.81 (d, 6.0 Hz, 3H, 9-C<u>H</u>$_3$); MS (CI-NH_3) *m/z* 236.0197 (MNH_4^+). Anal. Calcd for $C_{11}H_{19}O_2Cl$: C, 60.40; H, 8.76. Found: C, 60.73; H, 8.73.

Dimenthyl hydrazodicarboxylate (17)

To triethylamine (28.6 mL, 205 mmol), in dry THF (100 mL) at 0 °C, was added hydrazine (2.95 mL, 93 mmol) and the mixture was stirred until a cloudy solution appeared . Compound **16** (40.6 g, 186 mmol) was added and a white precipitate was formed. The mixture was stirred at 0 °C for 45 min and then at 20 °C for 24 h. The precipitate was filtered to yield a pale yellow white solid. This was recrystallised from $CHCl_3$ to yield 15.1 g (41% yield) of a white solid **17**: mp 108 - 110 °C; IR ($CHCl_3$ cast) 3283, 2954, 2919, 1707, 1493, 1241, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (bs, 2H, N<u>H</u>) 4.63 (dt, 4.0, 9.0 Hz, 2H, C<u>H</u>O), 2.06 (m, 2H), 1.92 (m, 2H), 1.67 (m, 4H), 1.47 (m, 2H), 1.33 (m, 2H), 1.04 (m, 6H), 0.91 (d, 6.5 Hz, 6H), 0.88 (d, 6.5 Hz, 6H), 0.79 (d, 7.0 Hz, 6H); MS (CI-NH_3) *m/z* 414.1524 (MNH_4^+). Anal. Calcd for $C_{22}H_{40}N_2O_4$: C, 66.63; H, 10.17; N, 7.06. Found: C, 66.27; H, 9.94; N, 6.80.

Dimenthyl azodicarboxylate (18)

This compound was prepared according to a modification of the method of Carpino and coworkers.[131] To compound **17** (2.38 g, 6.00 mmol) in THF (130 mL)was added pyridine (0.730 mL, 9.00 mmol). This was cooled and stirred at 0 °C and N-bromosuccinimide[130] (1.28 g, 7.20 mmol) was added, at which point the solution turned orange. This was covered in aluminium foil and stirred at 20 °C for 22 h. The reaction

mixture was washed with water (100 mL), and 10% K_2CO_3 (2 x 100 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield 2.24 g of a yellow orange solid, which was purified by flash chromatography (98:2 $CHCl_3$:MeOH) to yield 2.04 g (86% yield) of a yellow solid **18**: mp 66 - 69 °C; IR ($CHCl_3$ cast) 2959, 1771, 1455, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (dt, 5.0, 11.0 Hz, 2H, C<u>H</u>O), 2.17 (m, 2H), 1.98 (m, 2H), 1.72 (m, 4H), 1.54 (m, 4H), 1.14 (m, 6H), 0.95 (d, 8.5 Hz, 6H), 0.92 (d, 8.5 Hz, 6H), 0.82 (d, 7.0 Hz, 6H); MS (CI-NH_3) *m/z* 412.4627 (MNH_4^+). Anal. Calcd for $C_{22}H_{38}N_2O_4$: C, 66.96; H, 9.71; N, 7.10. Found: C, 66.22; H, 9.65; N, 7.02.

Ethyl 2-[N,N'-Bis(menthyloxycarbonyl)-hydrazino]-2-phenylacetate (23)

This compound was prepared according to the modification of the methods of Trimble and Vederas,[52] and Evans and coworkers.[159] Ethyl phenylacetate (0.159 mL, 1.00 mmol) was added dropwise to a cooled (-78 °C) solution of lithium hexamethyldisilazide (from $HN(SiMe)_3)_2$ (0.232 mL, 1.10 mmol), BuLi (1.49M, 0.67 mL, 1.00 mmol), THF (5 mL), -78 °C). The solution was stirred at -78 °C for 15 min, and a solution of **18** (0.394 g, 1.00 mmol) in THF (2 mL) was added over 5 min. The reaction mixture was stirred for 2 min and quenched at -78 °C with acetic acid (0.057 mL, 1.00 mmol). This was allowed to warm to 20 °C over 1 h and water (15 mL) was added. The resulting solution was extracted (3 x 15 mL) with CH_2Cl_2. The organic phases were combined, dried, and concentrated in vacuo to yield 0.599 g of a yellow liquid, which was purified by flash chromatography (85:15 Hexane:EtOAc) to yield 0.327 g (59% yield) of a colorless viscous liquid **23** as a 2:1 mixture of diastereomers: IR ($CHCl_3$ cast) 3230, 2955, 1737, 1713, 1206, 1040 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) [major diastereomer] δ 7.40 - 7.07 (m, 5H, Ar<u>H</u>), 6.59 (s, 1H, N<u>H</u>), 6.04 (s, 1H, C<u>H</u>CO_2), 4.75 (m, 1H), 4.44 (m, 1H), 4.01 (q, 2H,C<u>H</u>$_2$$CH_3$), 2.17 (m, 1H), 2.05 (m, 1H), 1.93 (b, 1H), 1.76 (b, 1H), 1.53 (m, 4H), 1.34 (m, 2H), 1.17 (m, 2H), 1.02 (m, 4H), 0.95

(d, 7.0 Hz, 3H), 0.91 (d, 7.0 Hz, 3H), 0.89 - 0.69 (m, 14H), 0.66 (d, 7.0 Hz, 3H); [minor diastereomer] δ 7.40 - 7.07 (m, 5H, ArH), 6.62 (s, 1H, NH), 6.09 (s, 1H, $CHCO_2$), 4.75 (m, 1H), 4.44 (m, 1H), 4.01 (q, 2H, CH_2CH_3), 2.17 (m, 1H), 2.05 (m, 1H), 1.93 (b, 1H), 1.76 (b, 1H), 1.53 (m, 4H), 1.34 (m, 2H), 1.17 (m, 2H), 1.02 (m, 4H), 0.95 (d, 7.0 Hz, 3H), 0.91 (d, 7.0 Hz, 3H), 0.89 - 0.69 (m, 14H), 0.66 (d, 7.0 Hz, 3H); MS (CI-NH_3) *m/z* 559.0319 (MH_4^+).

Diethyl [N,N'-Bis(menthyloxycarbonyl)-hydrazino] succinate (24)

This compound was prepared according to a modification of the methods of Trimble and Vederas,[52] and Evans and coworkers.[159] A solution of diethyl succinate (0.166 mL, 1.00 mmol) in THF (2 mL), was added dropwise to a cooled (-78 °C) solution of lithium hexamethyldisilazide (from $HN(SiMe)_3)_2$ (0.232 mL, 1.10 mmol), BuLi (1.49M, 0.67 mL, 1.00 mmol), THF (5 mL), -78 °C). The solution was stirred at -78 °C for 30 min, and a solution of **18** (0.394 g, 1.00 mmol) in THF (5 mL) was added over 5 min. The reaction mixture was stirred for 2 min and quenched at -78 °C with acetic acid (0.057 mL, 1.00 mmol). The mixture was allowed to warm to 20 °C over an hour and water (15 mL) added. The resulting solution was extracted (3 x 15 mL) with CH_2Cl_2. The organic phases were combined, dried, and concentrated in vacuo to yield 0.422 g of a yellow liquid, which was purified by repeated flash chromatography (80:20 Hexane:EtOAc) to yield 0.072 g (13% yield) of a colorless viscous liquid **24** as a 1:1 mixture of diastereomers: IR ($CHCl_3$ cast) 3310, 2955, 2870, 1740, 1370, 1270, 1040 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) [isomer A] δ 6.44 (s, 1H, NH), 5.45 (t, 6.5 Hz, 1H, CH_2CH), 4.73 (m, 2H), 4.09 - 3.94 (m, 4H, OCH_2CH_3), 3.02 (d, 7.0 Hz, 2H, CH_2CH), 2.04 (m, 2H), 1.55 (m, 4H), 1.33 (m, 4H), 1.08 (m, 3H), 1.02 (m, 6H), 0.99 - 0.86 (m, 15H), 0.86 - 0.77 (m, 8H); [isomer B] δ 6.44 (s, 1H, NH), 5.39 (t, 6.5 Hz, 1H, CH_2CH), 4.73 (m, 2H), 4.09 - 3.94 (m, 4H, OCH_2CH_3), 3.01 (d, 7.0 Hz, 2H,

CH_2CH), 2.04 (m, 2H), 1.55 (m, 4H), 1.33 (m, 4H), 1.08 (m, 3H), 1.02 (m, 6H), 0.99 - 0.86 (m, 15H), 0.86 - 0.77 (m, 8H); MS (CI-NH_3) *m/z* 586.6954 (MH_4^+).

Bornyl chloroformate (26)

A procedure similar to that used to prepare **16** was followed using borneol (10.0 g, 65.0 mmol), phosgene (4.94 mL, 71.0 mmol, d 1.432), triethyl amine (9.07 mL, 65.0 mmol). A quantitative yield of a yellow orange viscous liquid **26** was obtained. ^1H NMR showed the compound decomposes on standing: IR ($CHCl_3$ cast) 2960, 1775, 1700, 1172, 1151 cm^{-1}; MS (CI-NH_3) *m/z* 224.2977 (MH_4^+).

Dibornyl hydrazodicarboxylate (27)

A procedure similar to that used to prepare **17** was followed using compound **26** (14.3 g, 69.0 mmol), triethylamine (10.7 mL, 76.0 mmol), hydrazine hydrate (1.10 mL, 35 mmol). The product was purified by flash chromatography (98:2 $CHCl_3$:MeOH) to yield 7.50 g (55% yield) of a colorless liquid **27**: IR ($CHCl_3$ cast) 3290, 2954, 1718, 1482, 1454, 1230, 1062 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.70 (s, 2H, NH), 4.88 (m, 2H, $CHCO_2$), 2.34 (m, 2H), 1.88 (m, 2H), 1.70 (m, 4H), 1.25 (m, 4H), 1.09 (m, 2H), 0.92 - 0.79 (m, 18H); MS (CI-NH_3) *m/z* 410.4313 (MH_4^+); Anal. Calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 66.95; H, 9.38; N,6.55.

Dibornyl azodicarboxylate (28)

This compound was prepared according to the method of Carpino and coworkers.[131] To compound **27** (0.392 g, 1.00 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.121 mL, 1.50 mmol). This was cooled to 0 °C and N-bromosuccinimide (0.214 g, 1.20 mmol) was added at which point the solution turned orange. This was covered in aluminium foil and stirred at 0 °C for 1 h and at 20 °C for 26 h. The reaction mixture was washed with water (20 mL) and 10% K_2CO_3 (2 x 20 mL). The organic

phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield 0.307 g of a yellow-orange viscous liquid, which was purified by flash chromatography (98:2 $CHCl_3$:MeOH) to yield 0.299 g (77% yield) of a yellow solid **28**: mp 93 - 96 °C; IR ($CHCl_3$ cast) 2960, 1770, 1245, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (m, 2H, C<u>H</u>CO_2), 2.49 (m, 2H), 1.95 (m, 2H), 1.78 (m, 4H), 1.41 - 1.20 (m, 6H), 0.95 (s, 6H), 0.94 (s, 6H), 0.91 (s, 6H); MS (CI-NH_3) *m/z* 408.4650 (MNH_4^+).

Ethyl 2-[N,N'-Bis(bornyloxycarbonyl)-hydrazino]-2-phenylacetate (29)

A procedure similar to that used to prepare **23** was followed using ethyl phenylacetate (0.080 mL, 0.500 mmol), HMDS (0.116 mL, 0.550 mmol), BuLi (1.6 M, 0.312 mL, 0.500 mmol), and **28** (0.195 g, 0.51 mmol). The product was purified by flash chromatography (80:20 Hexane:EtOAc) to yield 0.158 g (57% yield) of a colorless viscous substance **29**: IR ($CHCl_3$ cast) 3330, 2950, 1734, 1719, 1388, 1210, 1021 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 7.40 – 7.09 (m, 5H, Ar<u>H</u>), 6.78 (s, 1H, N<u>H</u>), 6.11 (s, 1H, C<u>H</u>CO_2), 5.07 (m, 1H), 4.78 (m, 1H), 4.00 (q, 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.34 (m, 1H), 2.09 (m, 2H), 1.82 (m, 1H), 1.66 (m, 2H), 1.52 (m, 1H), 1.46 (m, 1H), 1.28 (m, 3H), 1.15 (m, 3H), 0.96 (t, 7.0 Hz, 3H, $CH_2C\underline{H}_3$), 0.89 (s, 3H), 0.81 (s, 3H), 0.77 (s, 6H), 0.73 (s, 3H), 0.69 (s, 3H); MS (CI-NH_3) *m/z* 555.4939 (MH_4^+).

Diethyl [N,N'-Bis(bornyloxycarbonyl)-hydrazino] succinate (30)

A procedure similar to that used to prepare **24** was followed using diethyl succinate (0.083 mL, 0.500 mmol), HMDS (0.116 mL, 0.550 mmol), n-BuLi (1.6 M, 0.312 mL, 0.500 mmol), and **28** (0.195 g, 0.510 mmol). The product was purified by flash chromatography (80:20 Hexane:EtOAc) to yield 0.139 g (49% yield) of a colorless viscous substance (**30**) shown to be a 1:1 mixture of diastereomers by ^1H NMR: IR ($CHCl_3$ cast) 3300, 2950, 1739, 1388, 1230, 1030 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) [Isomer A] δ 6.56 (s, 1H, N<u>H</u>), 5.35 (t, 6.5 Hz, 1H, $CH_2C\underline{H}$), 5.01 (m,

1H), 4.97 (m, 1H), 4.02 - 3.91 (m, 4H, $C\underline{H}_2CH_3$), 2.98 (d, 4.0 Hz, 2H, $C\underline{H}_2CH$), 2.27 (m, 2H), 1.99 (m, 2H), 1.64 (m, 2H), 1.49 (m, 2H), 1.29 - 1.03 (m, 6H), 1.01 - 0.95 (m, 9H), 0.83 (t, 7.0 Hz, 6H, $CH_2C\underline{H}_3$) 0.76 - 0.69 (m 9H); [Isomer B] δ 6.56 (s, 1H, N$\underline{H}$), 5.34 (t, 6.5 Hz, 1H, $CH_2C\underline{H}$), 5.01 (m, 1H), 4.97 (m, 1H), 4.02 - 3.91 (m, 4H, $C\underline{H}_2CH_3$), 2.96 (d, 4.0 Hz, 2H, $C\underline{H}_2CH$), 2.27 (m, 2H), 1.99 (m, 2H), 1.64 (m, 2H), 1.49 (m, 2H), 1.29 - 1.03 (m, 6H), 1.01 - 0.95 (m, 9H), 0.83 (t, 7.0 Hz, 6H, $CH_2C\underline{H}_3$) 0.76 - 0.69 (m, 9H); MS (CI-NH_3) *m/z* 582.7633 (MH_4^+).

L-Isoborneol (32)

D-Camphor (**31**) (30.0 g, 197 mmol) was dissolved in MeOH (300 mL) and cooled to 0 °C and sodium borohydride (16.4 g, 433 mmol) was added slowly over 30 - 45 min. The reaction mixture was stirred at 20 °C for 45 h, and water (200 mL) was added followed by saturated NH_4Cl (300 mL). The reaction was extracted (3x300 mL) with CH_2Cl_2, the organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield 30.7 g of a white solid. This mixture was purified by flash chromatography (90:10 Hexane:EtOAc) to yield 22.2 g (73% yield) of a white solid **32**: mp 214 - 216 °C; IR ($CHCl_3$ cast) 3400, 2950, 2875, 1450, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (m, 1H, C$\underline{H}$OH), 1.70 (m, 3H), 1.62 (m, 1H), 1.58 (s, 1H), 1.47 (dt, 5.0 Hz, $CH_2C\underline{H}CH_2$), 1.00 (s, 3H), 0.96 (m, 1H), 0.88 (s, 3H), 0.81 (s, 3H); exact mass 154.1357 (154.1357 calcd for $C_{10}H_{18}O$)

Isobornyl chloroformate (33)

A procedure similar to that used to prepare **16** was followed using isoborneol (**32**) (10.0 g, 65.0 mmol), phosgene (4.93 mL, 71.0 mmol, d 1.432), and triethylamine (9.98 mL, 71 mmol) to yield 11.2 g (80% yield) of a yellow liquid **33**: IR ($CHCl_3$ cast) 2958, 1776, 1458, 1155, 1044 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.75 (dd, 3.5, 7.5 Hz, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.72 (m, 2H), 1.12 (m, 2H), 1.03

(s, 1H), 0.98 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H); exact mass 216.0904 (216.0917 calcd for $C_{11}H_{17}O_2Cl$).

Diisobornyl hydrazodicarboxylate (34)

A procedure similar to that used to prepare **17** was followed using compound **33** (12.0 g, 56.0 mmol), triethylamine (8.51 mL, 61.0 mmol), and hydrazine hydrate (0.881 mL, 28 mmol). The product was purified by flash chromatography (98:2 $CHCl_3$:MeOH) to yield 6.05 g (55% yield) of a colorless liquid **34**: IR ($CHCl_3$ cast) 3283, 2953, 1715, 1455, 1227, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (bs, 2H, NH), 4.65 (bs, 2H, $CHCO_2$), 1.80 (m, 3H), 1.69 (m, 6H), 1.51 (m, 2H), 1.12 (m, 3H), 1.01(s, 3H), 0.94 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H), 0.85 (d, 4.5 Hz, 6H); MS (CI-NH_3) *m/z* 410.3283 (MH_4^+); Anal. Calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.52; H, 8.90; N, 7.23.

Diisobornyl azodicarboxylate (35)

A procedure similar to that used to prepare **28** was followed using compound **34** (2.80 g, 7.14 mmol), pyridine (0.890 mL, 11.0 mmol), and N-bromo succinimide (1.52 g, 8.60 mmol). The product was purified by flash chromatography (98:2 $CHCl_3$:MeOH) to yield 2.53 g (91% yield) of a yellow orange liquid **35**: IR ($CHCl_3$ cast) 2957, 1777, 1234, 1188, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, 3.5, 7.5 Hz, 2H, $CHCO_2$), 1.93 (m, 4H), 1.82 (m, 2H), 1.74 (m, 2H), 1.64 (m, 2H), 1.15 (m, 4H), 0.96 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.86 (d, 6H); MS (CI-NH_3) *m/z* 408.2306 (MNH_4^+); Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.36; H, 8.58; N, 6.99.

Ethyl 2-[N,N'-Bis(isobornyloxycarbonyl)-hydrazino]-2-phenylacetate (36)

A procedure similar to that used to prepare **23** was followed using ethyl phenylacetate (0.096 mL, 0.600 mmol), HMDS (0.139 mL, 0.660 mmol), BuLi (1.34 M, 0.492 mL, 0.660 mmol), and **35** (0.258 g, 0.660 mmol). The product was purified by flash chromatography (80:20 Hexane:EtOAc) to yield 0.138 g (42% yield) of a colorless viscous substance **36** which was shown to be a 1:1 mixture of diastereomers by ^{1}H NMR: IR ($CHCl_3$ cast) 3320, 2953, 1734, 1716, 1455, 1208, 1060 cm^{-1}; ^{1}H NMR (400 MHz, toluene d_8, 373 °K) [Isomer A] δ 7.36 – 7.02 (m, 5H, ArH), 6.57 (s, 1H, NH), 6.04 (s, 1H, $CHCO_2Et$), 4.76 (m, 1H), 4.49 (m, 1H), 3.96 (m, 2H), 1.86 (m, 2H), 1.71 (m, 2H), 1.58 - 1.41 (m, 6H), 1.41 - 1.18 (m, 4H), 1.01 (s, 3H), 0.96 - 0.90 (m, 6H), 0.83 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H), 0.68 (s, 3H); [Isomer B] δ 7.36 – 7.02 (m, 5H, ArH), 6.56 (s, 1H, NH), 6.04 (s, 1H, $CHCO_2Et$), 4.76 (m, 1H), 4.38 (m, 1H), 3.96 (m, 2H), 1.86 (m, 2H), 1.71 (m, 2H), 1.58 - 1.41 (m, 6H), 1.41 - 1.18 (m, 4H), 1.01 (s, 3H), 0.96 - 0.90 (m, 6H), 0.83 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H), 0.68 (s, 3H); MS (CI-NH_3) *m/z* 572.5842 (MH_4^+).

Diethyl [N,N'-Bis(isobornyloxycarbonyl)-hydrazino] succinate (37)

A procedure similar to that used to prepare **24** was followed using diethyl succinate (0.085 mL, 0.510 mmol), HMDS (0.118 mL, 0.560 mmol), n-BuLi (1.34 M, 0.380 mL, 0.510 mmol), and **35** (0.199 g, 0.510 mmol). The product was purified by flash chromatography (80:20 Hexane:EtOAc) to yield 0.117 g (41% yield) of a colorless viscous substance (**37**) which was shown to be a 1:1 mixture of diastereomers by ^{1}H NMR: IR ($CHCl_3$ cast) 3300, 2960, 1737, 1224, 1025 cm^{-1}; ^{1}H NMR (400 MHz, toluene d_8, 373 °K) [Isomer A] δ 6.44 (s, 1H, NH), 5.35 (m, 1H, $CHCH_2$), 4.75 - 4.64 (m, 2H), 4.03 - 3.89 (m, 4H, OCH_2CH_3), 2.96 (d, 7.0 Hz, 2H, $CHCH_2$), 1.84 (m, 3H), 1.67 (m, 3H), 1.53 (m, 5H), 1.39 (m, 3H), 1.00 - 0.96 (m, 6H), 0.92 (s, 3H), 0.91 - 0.88 (m, 6H), 0.73 (s, 6H); [Isomer B] δ 6.42 (s, 1H, NH), 5.35 (m, 1H, $CHCH_2$), 4.75

- 4.64 (m, 2H), 4.03 - 3.89 (m, 4H, $GC\underline{H_2}CH_3$), 2.96 (d, 7.0 Hz, 2H, $CHC\underline{H_2}$), 1.84 (m, 3H), 1.67 (m, 3H), 1.53 (m, 5H), 1.39 (m, 3H), 1.00 - 0.96 (m, 6H), 0.92 (s, 3H), 0.91 - 0.88 (m, 6H), 0.73 (s, 6H); MS (CI-NH_3) *m/z* 582.5580 (MH_4^+).

(R)-3-(1-oxopropyl)-4-isopropyloxazolidin-2-one (39)

The compound was prepared according to the procedure of Evans and coworkers,[144] from propionyl chloride (1.30 mL, 15.0 mmol), and (R)-4-isopropyl oxazolidin-2-one (2.00 g, 15.0 mmol) to give 2.29 g (83% yield) of **39** as a colorless oil: IR ($CHCl_3$ cast) 2960, 1781, 1703, 1460, 1206, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.42 (dt, 8.5, 3.6 Hz, 1H), 4.31 (t, 8.5 Hz, 1H), 4.26 (dd, 9.5, 3.2 Hz, 1H), 2.96 (m, 2H), 2.39 (m, 1H), 1.18 (t, 7.5 Hz, 3H), 0.92 (d, 7.0 Hz, 3H), 0.88 (d, 7.0 Hz, 3H); exact mass 185.1052 (185.1052 calcd for $C_9H_{15}NO_3$).

[2S,4S]-3-(1-oxo-2-[N,N'-Bis(isobornyloxycarbonyl)-hydrazino]-propyl)-4-isopropyloxazolidin-2-one (40)

The compound was prepared according to the procedure of Trimble and Vederas,[52] from (S)-3-(1 oxopropyl)-4-isopropyloxalidin-2-one[143] (0.463 g, 2.50 mmol), diisopropylamine (0.448 mL, 3.20 mmol), n BuLi (2.5M, 1.28 mL, 3.2 mmol) and diisobornyl azodicarboxylate (**35**) (1.25 g, 3.20 mmol). The crude mixture was purified by flash chromatography (68:32 Hexane:EtOAc) to yield 0.810 g (56% yield) of **40** as a white solid: mp 82 - 84 °C; IR (CH_2Cl_2 cast) 3340, 2955, 1786, 1719, 1699, 1390, 1206, 1057 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.65 (b, 1H), 5.95 (q, 7.0 Hz, 1H), 4.74 (dt, 8.0, 4.0 Hz, 2H), 3.86 (dd, 8.5 Hz, 4.0 Hz, 1H), 3.46 (t, 9.0 Hz, 1H), 2.20 (m, 1H), 1.86 (m, 2H), 1.71 (m, 2H), 1.54 (d, 7.8 Hz, 3H), 1.52 (m, 4H), 1.39 (m, 2H), 1.10 (m, 1H), 1.05 (s, 3H), 1.02 (m, 1H), 0.99 (s, 3H), 0.96 (m, 1H), 0.93 (s, 3H), 0.92 (m, 1H), 0.90 (s, 3H), 0.85 (m, 1H), 0.74 (d, 7.0 Hz, 6H), 0.69 (d,

7.2 Hz, 3H), MS (CI-NH_3) *m/z* 593.53 (MH_4^+); Anal. Calcd for $C_{31}H_{49}N_3O_7$: C, 64.67; H, 8.58; N, 7.30. Found: C, 64.81; H, 8.69; N, 7.03.

[2R,4R]-3-(1-oxo-2-[N,N'-Bis(isobornyloxycarbonyl)-hydrazino]-propyl)-4-isopropyloxazolidin-2-one (41)

The compound was prepared according to a similar procedure to that used for **40** to yield 1.26 g (88% yield) of **41** as a white solid: mp 79 - 81 °C; IR ($CHCl_3$ cast) 3330, 2957, 1785, 1705, 1458, 1301, 1207, 1056 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.73 (b, 1H), 6.01 (bm, 1H), 4.78 (dt, 8.5, 4.0 Hz, 2H), 4.69 (bm, 1H), 3.86 (m, 1H), 3.60 (dd, 3.0, 9.0 Hz, 1H), 3.53 (dd, 4.0, 10.0 Hz, 1H), 2.21 (m, 1H), 1.83 (m, 2H), 1.71 (m, 2H), 1.52 (m, 4H), 1.53 (d, 7.0 Hz, 3H), 1.37 (m, 2H), 1.04 (s, 3H), 1.01 (m, 1H), 0.98 (s, 3H), 0.94 (m, 2H), 0.90 (s, 6H), 0.85 (m,1H), 0.73 (s, 6H), 0.70 (d, 7.0 Hz, 3H), 0.57 (d, 7.0 Hz, 3H), MS (CI-NH_3) *m/z* 593.52 (MH_4^+); Anal. Calcd for $C_{31}H_{49}N_3O_7$: C, 64.67; H, 8.58; N, 7.30. Found: C, 64.60; H, 8.60; N, 7.01.

2S-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]-1-propanoic acid (42).

The compound was prepared according to the procedure of Evans and coworkers.[145] To a 0.05 M solution of **40** (0.100 g, 0.170 mmol), in 3:1 THF:H_2O cooled to 0 °C, was added hydrogen peroxide (27.0 μL, 0.870 mmol), followed by aqueous lithium hydroxide (0.015g, 0.350 mmol, 1.30 mL) solution. The reaction mixture was stirred at 0 °C for 1 h, quenched with 10% excess 1.5N Na_2SO_3 (100 μL), and buffered to pH 10 with aqueous $NaHCO_3$. The THF was evaporated and the resulting solution was extracted (3 x 15 mL) with CH_2Cl_2. The organic layers were dried, and concentrated *in vacuo* to yield 0.076 g of a colorless foam, which after repeated purification on preparative thin layer chromatography yielded 0.021 g (27% yield) of a colorless substance **42**. IR ($CHCl_3$ cast) 3420, 2955, 1713, 1613, 1456, 1298, 1060 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.55 (b, 1H, NH), 4.74 (m, 1H), 4.71 - 4.57

(m, 2H), 1.84 (m, 2H), 1.71 (m, 2H), 1.53 (m, 4H), 1.39 (d, 7.0 Hz, 3H, $CHC\underline{H}_3$), 1.30 (m, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.74 (s, 3H), 0.73 (s, 3H); MS (CI-NH_3) *m/z* 559.0319 (MH^+).

Methyl 2S-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]-1-propionate (43).

The compound was prepared according to the combined procedure of Evans and coworkers[145] and Vogel.[146] To a 0.05 M solution of **40** (0.050 g, 0.090 mmol), in 3:1 THF:H_2O cooled to 0 °C, was added hydrogen peroxide (13.0 µL, 0.430 mmol), followed by lithium hydroxide (0.007g, 0.170 mmol, 0.70 mL) solution. The reaction mixture was stirred at 0 °C for 1 h. Ether (2 mL) were added followed by HCOOH (39.0 µL, 0.85 mmol). An etheral solution of freshly prepared diazomethane,[78] was added till the evolution of nitrogen ceased and the color of the solution was a pale yellow. The resulting solution was concentrated *in vacuo* to yield 0.059 g of a white substance, which was purified on normal thin layer chromatography (5 x 10 cm) plates (95:5 $CHCl_3$:MeOH) to yield 0.036 g (86% yield) of a colorless substance **43**: IR ($CHCl_3$ cast) 3320, 2960, 1740, 1715, 1480, 1220, 1070 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.37 (bs, 1H, $N\underline{H}$), 4.89 (b, 1H, $COC\underline{H}$), 4.72 (m, 2H), 3.30 (s, 3H, $OC\underline{H}_3$), 1.82 (m, 3H), 1.70 (m, 3H), 1.52 (m, 5H), 1.43 (d, 7.5 Hz, 3H, $CHC\underline{H}_3$), 1.36 (m, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.73 (s, 6H); MS (CI-NH_3) *m/z* 496.6621 (MH_4^+).

Methyl 2R-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]-1-propionate (44).

The compound was prepared according to the combined procedure of Evans and coworkers[145] and Vogel.[146] To a 0.05 M solution of substrate **41** (0.100 g, 0.170 mmol), in 3:1 THF:H_2O cooled to 0 °C, was added hydrogen peroxide (27.0 µL, 0.870 mmol), followed by lithium hydroxide (0.015g, 0.350 mmol, 1.30 mL) solution. The reaction mixture was stirred at 0 °C for 1 h, then quenched with 10% excess 1.5N Na_2SO_3 (100 µL), and buffered to pH 10 with aqueous $NaHCO_3$. The THF was evaporated and the

resulting solution was extracted (3 x 15 mL) with CH_2Cl_2. The organic layers were dried, and concentrated *in vacuo* to yield 0.092 g of a colorless foam, which was divided into two. The crude product (0.046 g, 0.080 mmol) was dissolved in ether (3 mL), followed by HCOOH (10.0 μL) and the resulting solution was cooled to 0 °C. An etheral solution of freshly prepared diazomethane [146] was added till the evolution of N_2 ceased and the color of the solution was a pale yellow. The resulting solution was concentrated *in vacuo* to yield 0.044 g of a white substance, which was purified on normal thin layer chromatography (5 x 10 cm) plates (95:5 $CHCl_3$:MeOH) to yield 0.034 g (87% yield) of a colorless substance **44**: IR ($CHCl_3$ cast) 3320, 2952, 1741, 1718, 1455, 1210, 1080 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.42 (bs, 1H, NH), 4.90 (b, 1H, COCH), 4.75 (m, 2H), 3.32 (s, 3H, OCH_3), 1.83 (m, 3H), 1.79 (m, 3H), 1.52 (m, 5H), 1.44 (d, 7.5 Hz, 3H, $CHCH_3$), 1.36 (m, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.74 (s, 3H), 0.72 (s, 3H); MS (CI-NH_3) *m/z* 496.0885 (MH_4^+).

S-(-)-α-Ureidopropionic acid (46)

The compound was prepared according to the procedure of Dakin.[149] L-alanine (**45**) (10.0 g, 112 mmol), and potassium cyanate (20.0 g, 247 mmol) were dissolved in water (40 mL), and heated to 80 °C for 1 h. The solution was acidifed to pH 4. The precipated product **46** was filtered, washed with cold water, and dried under vacuum to yield 10.7 g (72% yield): mp. 193-194 °C; [α] -7.665 (c=1.135 H_2O) {Lit [α] -7.9}; IR (KBr): 3458, 3313, 1701, 1689, 1633, 1576 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 1.17(d, 7.3 Hz, 3H), 3.98 (q, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, D_2O); δ 16.66 (CH_3), 48.96 (CH), 160.59 (NH-CO-NH_2), 177.75 (COOH); MS (POSFAB): 133.07 (MH^+).

S-(-)-α-Hydrazinopropionic acid (47)

The compound was prepared according to the procedure of Gustafasson.[68] S-(-)-α-Ureidopropionic acid **46** (2.29 g, 16.0 mmol) was dissolved in cold 2M NaOH (10 mL). A solution of 0.5 N NaOCl [160] was added dropwise, and the reaction mixture was stirred at 20 °C for 1.5 h. Hydrazine (1.6 mL, 50.5 mmol) was added to destroy the excess NaOCl. The pH was adjusted to 3 and the water was removed in vacuo at 50 °C. The residue was suspended in acetic acid and the NaCl was filtered. A precipitate was obtained with $CHCl_3$, which was filtered and freeze dried. This was then dissolved in water and recrystallized from MeOH to yield 0.550 g (39% yield) of **47** as a white solid: mp 212-213 °C (lit mp 211-213 °C); [α] -27.46 (c=0.976 6M HCl); {lit [α] -30 (c=0.964 6M HCl)} IR (KBr): 3325, 2870, 1666, 1624, 1572,1475, 1339 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.20(d, 7.6 Hz, 3H), 3.19 (q, 7.6 Hz, 1H); MS (POSFAB): 105.28 (MH^+).

Methyl 2S-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]-1-propionate (48).

The 2S-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]-1-propanoic acid was prepared according to the combination procedure of Arnold[150] and Fujino and coworkers.[136] Compound **47** (0.082 g, 0.790 mmol) was dissolved in a cooled 1M $NaHCO_3/Na_2CO_3$ solution and THF (1.5 mL) added. Isobornyl chloroformate **33** (0.427 g, 1.97 mmol) in dioxane (2mL) was added and the mixture was stirred at 20 °C for 5h. The solution was acidified to pH 2 and extracted (3 x 5 mL) with EtOAc. The organic layers were combined, dried, and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (90:10 $CHCl_3$:MeOH) to yield 0.060 g (16% yield) of the acid. The acid (0.020 g, 0.043 mmol), was suspended in ether (5 mL). A freshly prepared ether solution of diazomethane[146] was added till the solution was yellow, and the mixture was stirred at 20 °C overnight. The excess diazomethane was destroyed with CH_3COOH, and the solution was concentrated *in vacuo*, and purified by flash

chromatography (90:10 Hexane:EtOAc) to yield 0.019 g of **48** (91% yield) as a white solid:[α] -56.9 (c=0.822 $CHCl_3$); IR ($CHCl_3$ cast) 2953, 1742, 1716, 1297, 1213, 1060 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) δ 6.37 (bs, 1H, NH), 4.88 (b, 1H, COCH), 4.71 (m, 2H), 3.31 (s, 3H, OCH_3), 1.82 (m, 3H), 1.70 (m, 3H), 1.53 (m, 5H), 1.43 (d, 7.5 Hz, 3H, $CHCH_3$), 1.36 (m, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.73 (s, 6H); MS (CI-NH_3) *m/z* 496.15 (MH_4^+).

N,N-Dimethylpropionamide (49)

To a cooled solution of propionyl chloride (8.69 mL, 100 mmol) in THF (120 mL), was added dimethylamine (13.5 mL, 300 mmol). A white solid precipated, and the resulting solution was stirred at 0 °C for 2 h. The solid was filtered, and the filtrate was concentrated in vacuo to yield 8.80 g (87% yield) of a liquid **49**: IR ($CHCl_3$ cast) 2930, 1648, 1510, 1460, 1396 cm^{-1}; ^1H NMR (200 MHz, toluene d_8) δ 2.66 (s, 3H), 2.35 (s, 3H), 1.89 (q, 8.0 Hz, 2H), 1.03 (t, 7.5 Hz, 3H); exact mass 101.0841 (101.0841 calcd for $C_5H_{11}NO$).

N,N-Dimethyl-2-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]propionamide (50)

The compound was prepared according to the procedure of Trimble and Vederas[52] from N,N-Dimethylpropionamide (0.126 g, 1.25 mmol), diisopropylamine (0.224 mL, 1.60 mmol), n-BuLi (2.4 M, 0.670 mL, 1.60 mmol), and diisobornyl azodicarboxylate (**35**) (0.627 g, 1.60 mmol). The crude reaction mixture was purified by flash chromatography (55:45 Hexane:EtOAc) to yield 0.442 g (72% yield) of **50** as a colorless substance was shown to be a 1:1 mixture of diastereomers by ^1H NMR: IR ($CHCl_3$ cast) 3280, 2953, 1733, 1709, 1649, 1458, 1226, 1060 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) [Isomer A] δ 7.14 (b, 1H, NH), 5.08 (b, 1H, $CHCONMe_2$), 4.71 (m, 2H), 2.53 (s, 3H, NCH_3), 2.52 (s, 3H, NCH_3), 1.85 (m, 2H), 1.69 (m, 3H),

1.53 (m, 5H), 1.38 (m, 4H), 1.28 (d, 7.0 Hz, 3H, $CHC\underline{H}_3$), 1.03 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H), 0.75 (s, 3H), 0.73 (s, 3H); [Isomer B] δ 7.14 (b, 1H, N$\underline{H}$), 5.08 (b, 1H, $C\underline{H}CONMe_2$), 4.71 (m, 2H), 2.53 (s, 3H, $NC\underline{H}_3$), 2.52 (s, 3H, $NC\underline{H}_3$), 1.85 (m, 2H), 1.69 (m, 3H), 1.53 (m, 5H), 1.38 (m, 4H), 1.26 (d, 7.0 Hz, 3H, $CHC\underline{H}_3$), 1.03 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H), 0.75 (s, 3H), 0.73 (s, 3H); MS (CI-NH_3) *m/z* 492.5781 (MH^+).

N,N-Dimethylisovaleramide (51)

The compound was prepared according to a procedure similar to that employed for **49** using isovaleryl chloride (6.10 mL, 50 mmol) and dimethylamine (6.76 mL, 150 mmol). The crude product was purified by flash chromatography (95:5 $CHCl_3$:MeOH) to yield 4.89 g (76% yield) of a pale yellow liquid **51**: IR ($CHCl_3$ cast) 2960, 1647, 1500, 1470, 1398, 1105 cm^{-1}; ^1H NMR (400 MHz, toluene d_8) δ 2.65 (s, 3H, $NC\underline{H}_3$), 2.37 (s, 3H, $NC\underline{H}_3$), 2.18 (m, 1H, $C\underline{H}(CH_3)_2$), 1.87 (d, 2H, $C\underline{H}_2NMe_2$), 0.90 (d, 6H, $CH(C\underline{H}_3)_2$); MS exact mass 129.1156 (129.1153 calcd for $C_7H_{15}NO$).

N,N-Dimethyl-2-[N,N'-Bis(isobornyloxycarbonyl)hydrazino]isovaleramide (52)

The compound was prepared according to the procedure of Trimble and Vederas[52] from N,N-Dimethylisovaleramide (**51**) (0.161 g, 1.25 mmol), diisopropyl amine (0.224 mL, 1.60 mmol), n BuLi (2.4 M, 0.670 mL, 1.60 mmol) and diisobornyl azodicarboxylate (**35**) (0.627 g, 1.60 mmol).The crude product was purified by flash chromatography (55:45 Hexane:EtOAc) to yield 0.566 g (87% yield) of **52** as a colorless substance which was shown to be a 1:1 mixture of diastereomers by ^1H NMR: IR ($CHCl_3$ cast) 3280, 2953, 1707, 1640, 1400, 1225, 1059 cm^{-1}; ^1H NMR (400 MHz, toluene d_8, 373 °K) [Isomer A] δ 4.86 (d, 9.0 Hz, 1H, $C\underline{H}CONMe_2$), 4.73 (m, 2H), 2.75 (b, 6H, $N(C\underline{H}_3)_2$), 2.32 (m, 1H, $CH(C\underline{H}_3)_2$), 1.84 (m, 5H), 1.53 (m, 6H), 1.39 (m, 3H), 1.03

(s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.74 (m, 12H); [Isomer B] δ 4.82 (d, 9.0 Hz, 1H, C<u>H</u>CONMe$_2$), 4.73 (m, 2H), 2.75 (b, 6H, N(C<u>H</u>$_3$)$_2$), 2.32 (m, 1H, CH(C<u>H</u>$_3$)$_2$), 1.84 (m, 5H), 1.53 (m, 6H), 1.39 (m, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.74 (m, 12H); MS CI-NH$_3$ *m/z* 520.3755 (MH$^+$).

Hydrazinopropionic acid (53)

The compound was prepared according to the procedure of Ito and coworkers[157] using **50** (0.038 g, 0.08 mmol) and 6N HCl (1.5 mL) to yield after AG-50X8 ion exchange chromatography 9 mg (75% yield) of **53** as its HCl salt: IR ($CHCl_3$ cast) 2962, 2778, 1728, 1580, 1243, 1082 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.80 (q, 1H, C<u>H</u>CH$_3$), 1.45 (d, 3H, CHC<u>H</u>$_3$); MS (POSFAB) *m/z* 105.16 (MH$^+$).

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