Asymmetric α-Amino Acid Synthesis

A Thesis
Submitted Towards the
Degree of
Doctor of Philosophy

by

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STATEMENT

To the best of my knowledge, this thesis contains no material previously submitted for a degree or diploma and contains no material previously published, except where due reference is made.

Pasquale Razzino (B. Sc. Hons.)

NAME: PASQUALE RAZZINO **COURSE:** PhD

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PUBLICATIONS

Some of the work described in this thesis has been reported in the following publications:

David P.G. Hamon, Pasquale Razzino and Ralph A. Massy-Westropp, *J. Chem Soc., Chem. Commun.*, **1991**, 332.

David P.G. Hamon, Ralph A. Massy-Westropp, and Pasquale Razzino, *J. Chem Soc., Chem. Commun.*, **1991**, 722.

ABSTRACT

The derivative of glycine, 8-phenylmenthyl *N*-*t*-Boc-glycinate (**47**), undergoes free radical bromination by *N*-bromosuccinimide to give 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate (**48**).

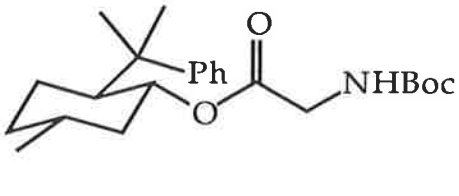
Treatment of the bromide (**48**) with a variety of Grignard reagents at low temperature gave 8-phenylmenthyl *N*-*t*-Boc-(*S*)-2-alkylglycinates with high diastereoselectivity. Conditions were found for the hydrolysis of these derivatives with no racemization of the resultant amino acid.

N.M.R. data indicated that the bromide (**48**) was produced as mainly one diastereomer. Since little research into asymmetric induction at radical centres in acyclic systems had been reported, radical reactions suitable for the elaboration of compound (**48**) were investigated.

Reduction of the bromide (**48**) with tri-*n*-butyldeuteriostannane gave the (*S*)-2-deuterioglcine derivative (**128a**) in high optical yield. Similar chemistry allowed the synthesis of the (*R*)-2-deuterioglycine derivative (**128b**). Hydrolysis of the derivative (**128a**) yielded (*S*)-2-deuterioglycine with little, if any, loss of deuterium.

Bromide (**48**) was also shown to react with a number of tri-*n*-butylallylstannanes, by allyl transfer to the intermediate radical (**120**), to give the corresponding unsaturated amino acid derivatives. These reactions proceeded with high diastereoselectivity to give mainly the 2-(*S*) isomer. Hydrolysis of 8-phenylmenthyl *N*-*t*-Boc-(*S*)-2-allylglycinate (**157a**), prepared in the above manner, proceeded with less than 2% racemization of the resultant (*S*)-allylglycine.

Bromide (48) reacted with propargyl- and allenyltriphenylstannanes to give, unexpectedly, the (2)-propargyl and (2)-allenyl derivatives (**169**) and (**172**) respectively. These reactions also proceeded with high diastereoselectivity to give mainly the 2-(*S*) isomer.



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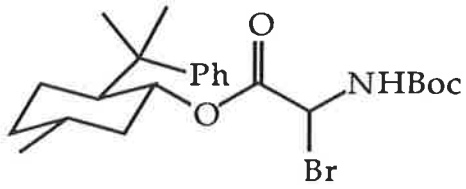

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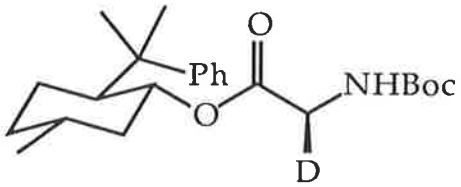

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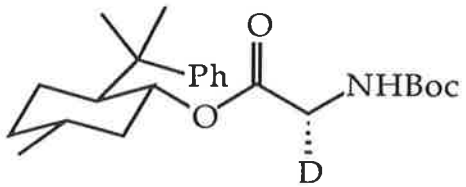

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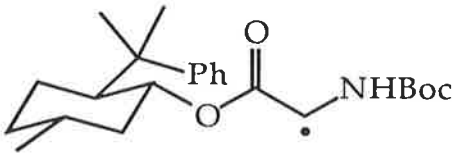

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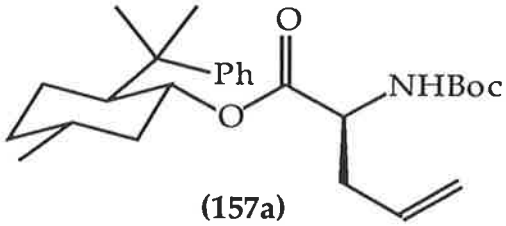

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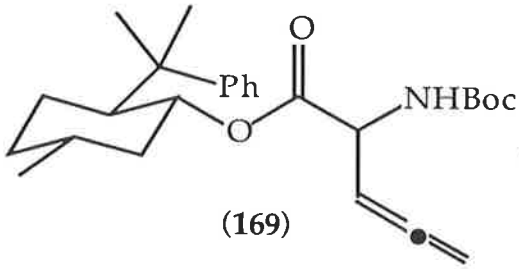

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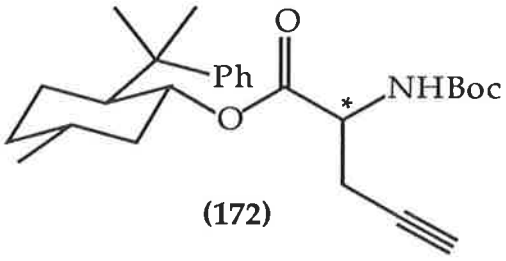

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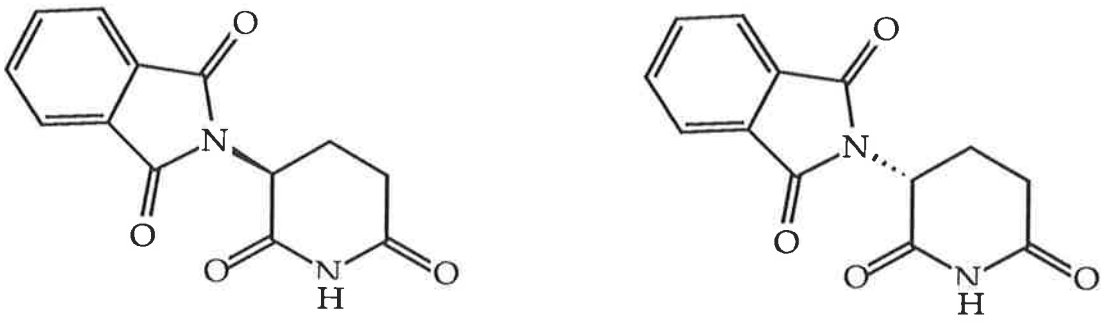
Chapter 1 - Introduction

Morrison and Mosher[1] defined an asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a way that the stereoisomeric products are produced in unequal amounts". Such a synthesis can be achieved with optically active substrates[2], reagents[3], catalysts[4] and solvents[5]. The kinetically controlled asymmetric induction reactions employing these methods all exploit the fact that the transition states which give rise to the alternative stereoisomers are diastereomeric (and hence energetically non-equivalent). If the difference in activation energies is large enough, a product of high optical purity results.

The sheer amount of research into asymmetric synthesis throughout the world is testimony to the fundamental importance of enantiomerically pure compounds in organic synthesis and in wider society. Enantioselective synthesis of organic compounds is an indispensible tool for the production of biologically active compounds, most notably in the pharmaceutical, food and agrochemical industries. Since the receptor sites in biological systems are themselves chiral, they are able to distinguish between the two enantiomeric forms of the compounds with which they interact. As this basic principle becomes further entrenched in the thinking of modern day chemists, optical purity becomes an increasingly important critereon in assessing the overall purity of a compound.

In the particular case of drugs, the ever increasing stringency of regulatory bodies with regard to enantiomeric purity has placed an even greater emphasis on asymmetric synthesis of therapeutic agents. This state of affairs is well justified when the potentially disastrous consequences of

administration of racemic drugs are considered. Perhaps the best known and most dramatic example of the differing biological activities of enantiomers is the case of the drug thalidomide, introduced in the early 1960's as a sedative and hypnotic. When administered in racemic form, it was found to cause foetal and neonatal deaths and congenital malformations when used by pregnant women[6]. These effects were later attributed to the (*S*)-(–) enantiomer (**1**)[7] (**Figure 1**). The sedative effect resides in the (*R*)-(+) enantiomer (**2**), which is otherwise innocuous.



(**1**) (**2**)

FIGURE 1

α–amino acids occur in nature as the monomeric building blocks of proteins and peptides, as constituents of more complex, non-proteinogenic biomolecules, and as the free monomer. All monosubstituted α-amino acids contain a chiral α-carbon about which are arranged the amino and carboxyl groups, the α-hydrogen and the "R" group or "side chain" which endows each amino acid with its unique properties. Those of natural origin almost invariably are optically pure, with the most common configuration being (*S*).

Today, the multi-billion dollar amino acid industry produces the twenty basic proteinogenic α-amino acids in optically pure form either by

extraction from protein hydrolysates, fermentation and enzymatic methods, or racemic chemical syntheses followed by resolution[8]. Apart from these common α-amino acids, there exist hundreds more non-proteinogenic, optically pure amino acids with modified or completely different side-chains[9]. These side-chains fall into a wide range of categories such as aliphatic, aromatic, heterocyclic, sulphur-containing, acidic and basic, to name but a few. Of these, many exhibit biological activity. As is usually the case with chiral, biologically active molecules, properties such as taste and therapeutic effectiveness are limited to, or significantly more pronounced in, one stereoisomer only. This is well illustrated by the example of the artificial sweetener known as aspartame. This molecule is the dipeptide methyl ester (**3**) (**Figure 2**), which consists of the amino acids (*S*)-phenylalanine and (*S*)-aspartic acid. Aspartame tastes about 160 times sweeter than sucrose. The diastereomer of aspartame which contains (*R*)-phenylalanine (**4**) is, in stark contrast, bitter tasting[10].

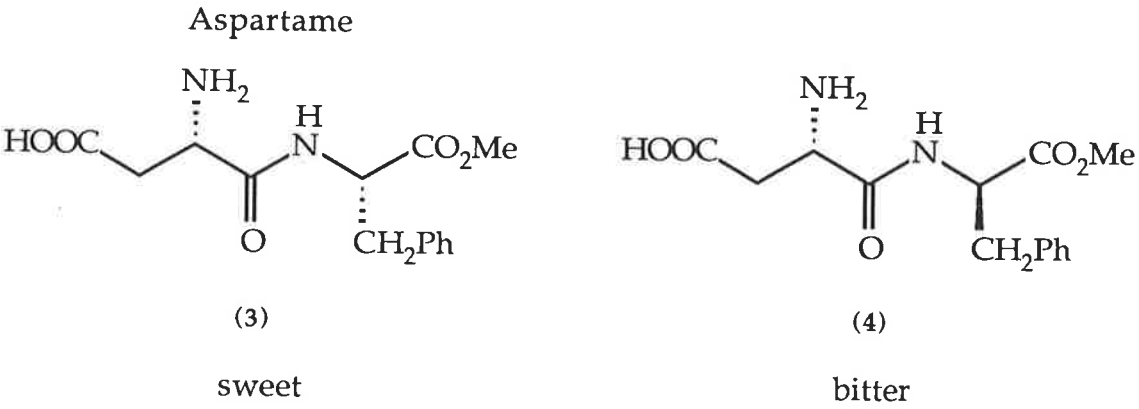


FIGURE 2

The classical techniques used to produce the common α-amino acids are not necessarily applicable to the rarer α-amino acids. Hence, as well as posing a challenging synthetic problem and providing access to useful quantities of novel amino acids for research purposes, the efficient

asymmetric synthesis of such amino acids has significant implications to the food, pharmacological and agrochemical industries. Thus, advances in asymmetric α-amino acid synthesis have the potential to ultimately improve human health and living standards.

As a result of these potential rewards, the field of asymmetric α-amino acid synthesis has grown steadily to the point where, today, most α-amino acid syntheses reported are stereoselective. Due to the sheer diversity of functionalities found in α-amino acid side-chains, an "all-encompassing" method for their asymmetric synthesis has not yet been developed, and, in all likelihood, never will be. Hence, the many methods which exist are necessarily very diverse.

Some of the more common approaches to asymmetric α-amino acid synthesis are summarized in **Figure 3**. Discussion of the various methods will be very brief, with the references given being exemplary only. Route **A** involves the asymmetric addition of a carbon nucleophile to a prochiral imine (**6**) (or iminium) species[11], or alkylation of a glycinyl anion (**7**) with a carbon electrophile[12]. Route **B** requires stereoselective hydrogenation of the imine (**8**)[13] or α-β-dehydro α-amino acid (**9**)[14]. Alternatively, asymmetric protonation of the α-amino ester enolate (**10**) has been exploited[15]. Route **C** can be realized by hydroformylation of the enamine (**11**)[16]. One approach to route **D** is the electrophilic amination of the ester enolate (**12**)[17,18]. Another approach is the nucleophilic amination of the α-substituted ester (**13**)[19,20], where the substituent X is a suitable leaving group. Transamination of the α-keto ester (**14**), a common strategy in biological systems, has also been used *in vitro*[21].

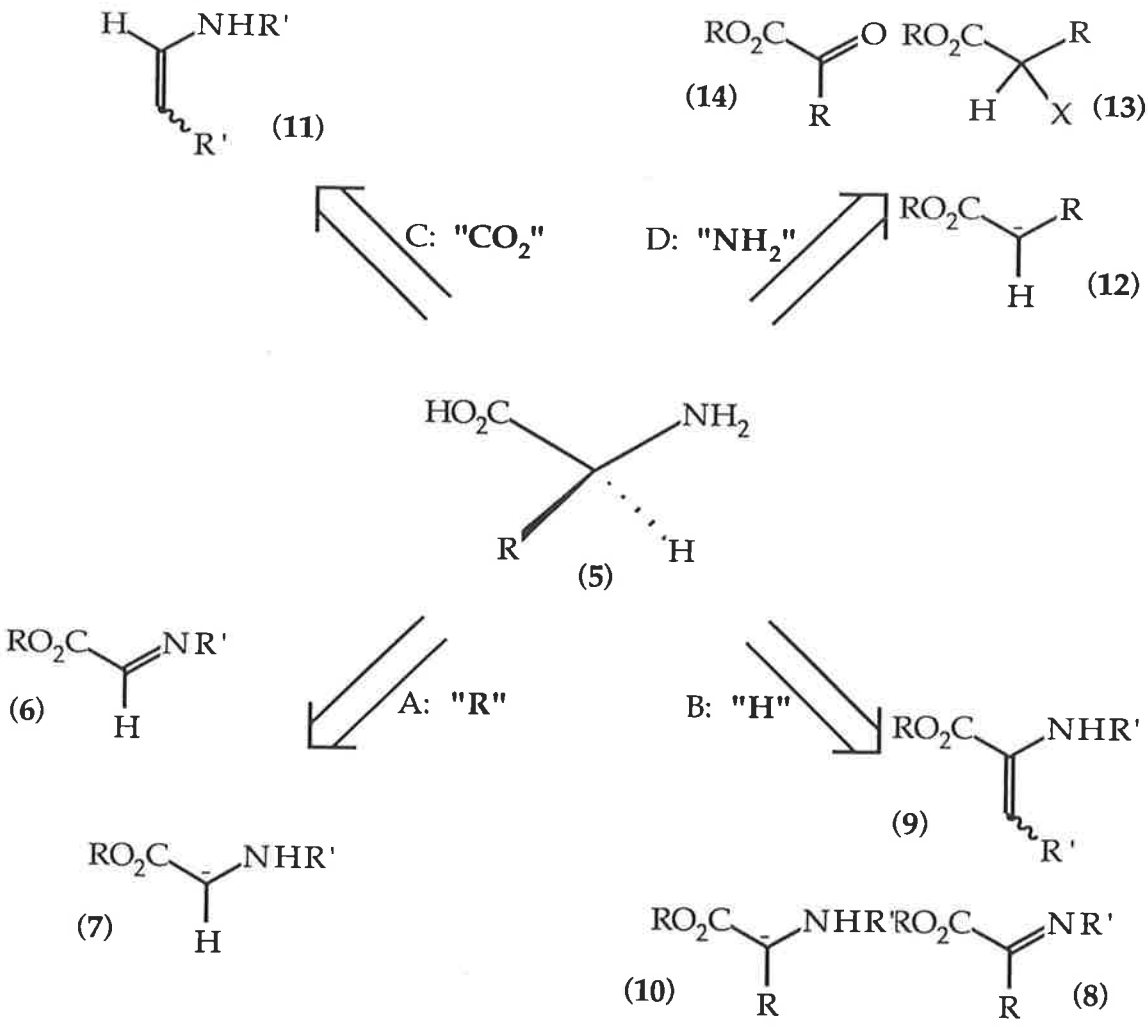
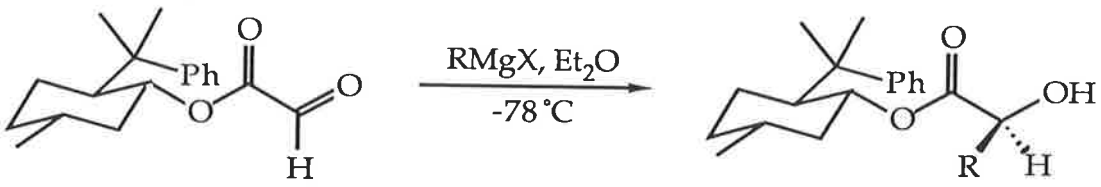


FIGURE 3

Thus, it can be seen that, with the number of possible approaches, coupled with the choice of a chiral auxiliary being situated at either the amino or carboxyl terminii as well as the potential for the use of chiral reagents and catalysts, a multitude of potential routes to optically pure α-amino acids exist. It is beyond the scope of this thesis to attempt to review the now large and rapidly growing volume of research into this area, which, in any case, has been reviewed elsewhere[22]. Hence, only literature reports directly related to the research undertaken here will be discussed.



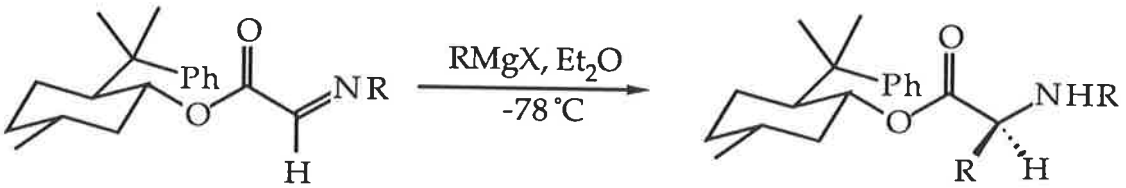
(15) **(16)**

R= Me, $Me(CH_2)_5$, $Me(CH_2)_7$, Ph, *c*-hex

d.e.= 98.1-99.4%

SCHEME 1

The initial approach to asymmetric α-amino acid synthesis described in this thesis was inspired by work reported by Whitesell in 1982[23], and later elaborated upon in 1985[24] and 1986[25]. In these publications, Whitesell reported that the glyoxylate ester of (–)-8-phenylmenthol (**15**) underwent highly regioselective and diasterioselective alkylation with several Grignard reagents (**Scheme 1**). At low temperature, nucleophilic attack by the organometallic species is selective for the aldehyde carbonyl. In addition, the glycolates (**16**) were formed with a very high (98.1-99.4%) excess of the 2-(*S*) isomer. The authors' rationalization of these results will be discussed at a more relevant point in this thesis.

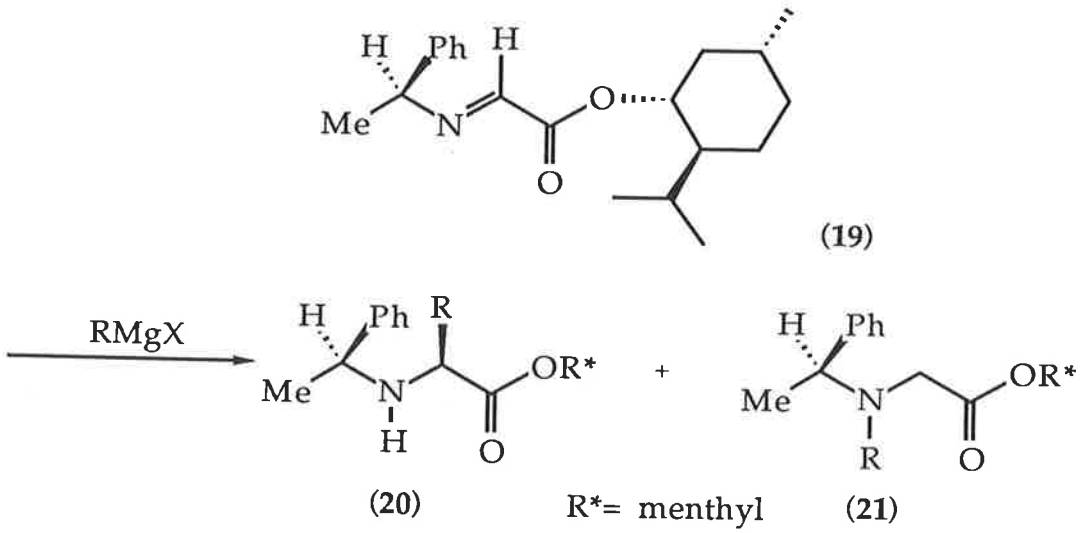


(17) **(18)**

SCHEME 2

The obvious analogy between the glyoxylate ester (**15**) and the imino ester (**17**) led to speculation whether Grignard addition to such an imine could be achieved with similar levels of asymmetric induction (**Scheme 2**). If so, and if removal of the chiral auxiliary could be achieved without

diminishment of the optical purity of the amino acid moiety of (**18**), then this approach to asymmetric α-amino acid synthesis would be relatively efficient and general.



SCHEME 3

Kagan and Fiaud[26] had reported this very same approach at a much earlier date. These workers added Grignard reagents to the prochiral imine (**19**) bearing chiral auxiliaries at both the imino and carboxyl sites (**Scheme 3**). With some Grignard reagents, the imine alkylated at the imino carbon, giving the amino esters (**20**) with a modest predominance of the (*S*) configuration at the α centre. Significantly, the authors found that, irrespective of the configuration of the nitrogen linked chiral auxiliary, the 2-(*S*) diastereomer was formed in excess, with little variation in the d.e. (diastereomeric excess).

This led the authors to conclude that the ester-linked chiral auxiliary (menthol) was chiefly responsible for the asymmetric induction observed. This, along with the demonstrable superiority of 8-phenylmenthol over

menthol as a chiral auxiliary, further reinforces that the alkylation of (**17**) is a viable approach to asymmetric α-amino acid synthesis.

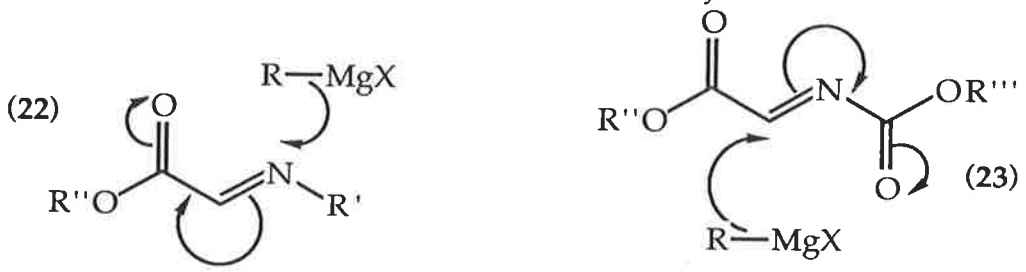


FIGURE 4

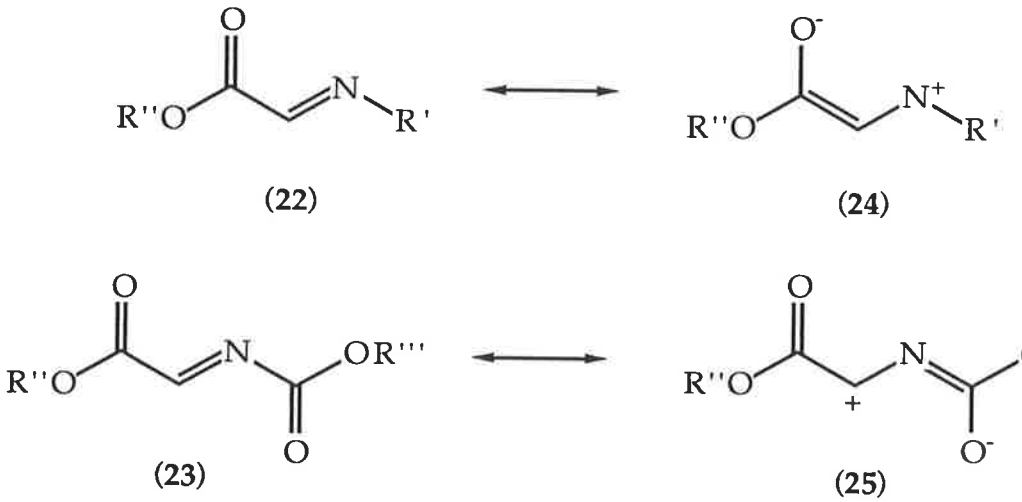
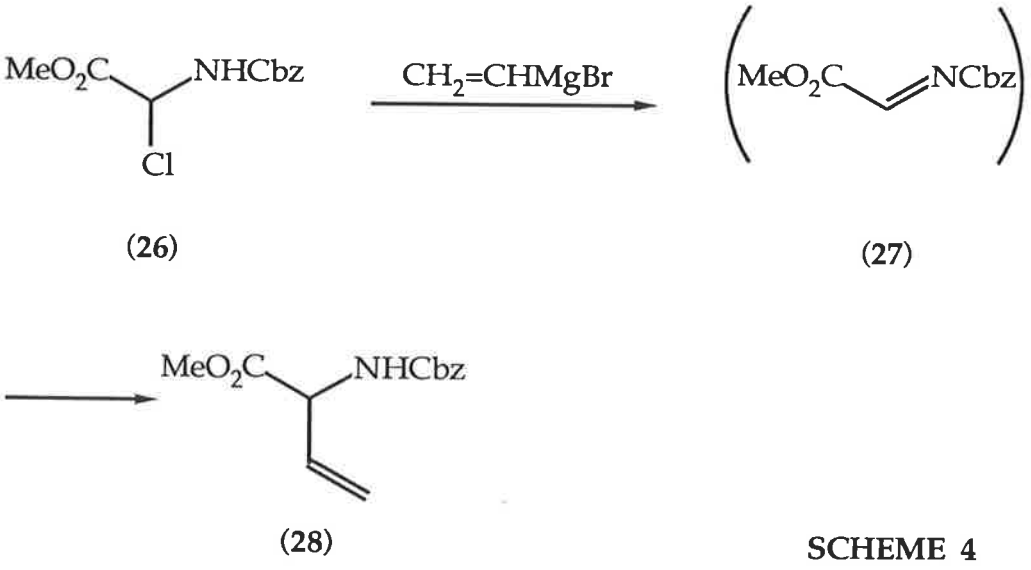


FIGURE 5

Most Grignard reagents used by Kagan and Fiaud, however, alkylated the imine at nitrogen to give chiefly (**21**). Yamamoto *et al.*[27] reinvestigated the alkylation of iminoacetates of this type. These workers reported that, in addition to competitive *N*-alkylation, allylmagnesium bromide also attacked the ester carbonyl. The most likely explanation for *N*-alkylation of this system is that conjugate 1,4 addition to the imine (**22**) competes with *C*-alkylation (1,2 addition to the imine double bond) (**Figure 4**) due to the fact that the resonance contributor (**24**) renders the imino nitrogen somewhat electrophilic (**Figure 5**). It was reasoned that the presence of an acyl group on the imino nitrogen would minimize (or hopefully

eliminate) *N*-alkylation due to the influence of the resonance contributor (**25**), which should enhance the electrophilicity of the α-carbon.



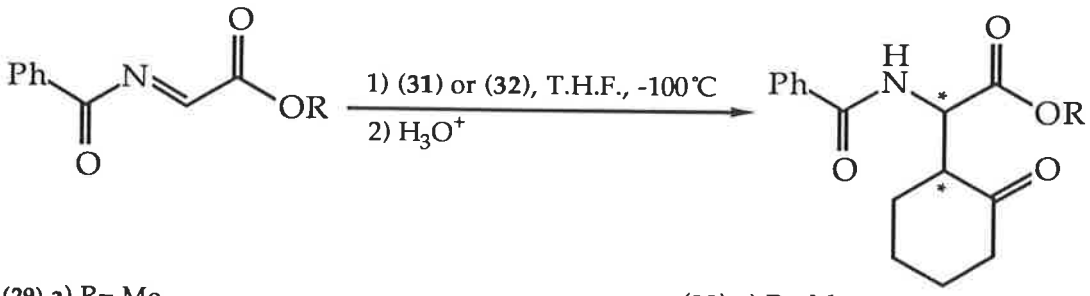
(**26**) (**27**) (**28**)

SCHEME 4

Castelhano *et al*[28] have reported the alkylation of the carbobenzyloxy (Cbz) protected α-chloro-α-amino ester (**26**) with two equivalents of vinylmagnesium bromide at –70°C (**Scheme 4**). The imine (**27**), produced by elimination of hydrogen chloride from (**26**), is thought to be the active species which undergoes Grignard addition. The authors stated that products of Grignard addition to the carbonyl groups of (**26**) were not detected, and made no mention of *N*-alkylation. The absence of *N*-alkylation in this case lends credence to the proposal that the electronic effect of the acyl group on nitrogen should promote *C*-alkylation by Grignard reagents.

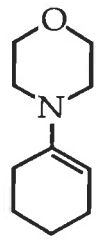
Enders and Steglich *et al*[29] also have employed the *C*-alkylation of acyliminoacetates as a means of asymmetric α-amino acid synthesis. Firstly, the achiral imine (**29a**) was found to react with the achiral enamine (**31**) at -100°C (**Scheme 5**) to give the α amino-γ-oxo acid ester (**30a**) with high diastereoselectivity (*anti* 2,3 stereochemistry). These results were

rationalized by assuming a Diels-Alder like transition state for the alkylation step.



(29) **a)** R= Me
b) R= (-)-8-phenylmenthyl
c) R= (+)-menthyl

(30) **a)** R= Me
b) R= (-)-8-phenylmenthyl
c) R= (+)-menthyl



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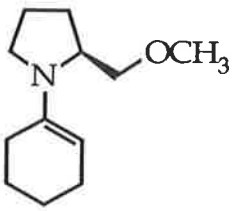
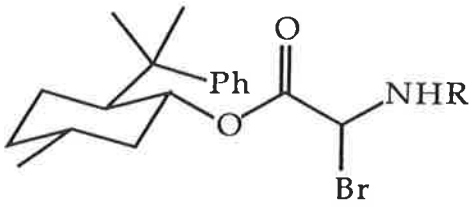


(32)

SCHEME 5

Next, the achiral imine (**29a**) was treated with the chiral enamine (**32**), and the chiral imine (**29b**) was treated with the achiral enamine (**31**), also resulting in high diastereoselectivity and now with modest (67-85%) e.e. (enantiomeric excess). Finally, double asymmetric reactions, with both imine (**29c**) and enamine (**32**) being chiral, were carried out. Here, both d.e. and e.e. were >99.9% when this matched chiral enamine/chiral imine pair was used.

These results are encouraging in that they set a precedent for the diastereoselective alkylation of prochiral α-acyliminoacetates. In particular, the ~~high~~ modest (67%) e.e. for the alkylation of (–)-8-phenylmenthyl 2-benzoyliminoacetate (**29b**), an example of the generalized imine (**17**), augured well for the success of our approach.



(33)

FIGURE 6

Substitution of a suitable leaving group for one of the hydrogen atoms at the α position of a glycine moiety would appear to be the most expedient and general route to an imine such as (**17**). Thus the bromide (**33**) (**Figure 6**), which is effectively the hydrogen bromide adduct of the corresponding imine, is ideally suited for Grignard alkylation in the same manner as the chloride (**26**), used by Castelhano.

Lidert and Gronowitz[30] first described a means of radical bromination of the α position of glycine derivatives with *N*-bromosuccinimide. Since then, a great deal of work has been published in which the authors have used bromination of amino acid derivatives with N.B.S. as a means of functionalizing the α position of such compounds[13,31,32,33,34]. Indeed, in the work of Enders and Steglich described above, the imines (**29**) were obtained by treatment of the corresponding α-bromides (obtained by free radical bromination of the parent glycine derivative with N.B.S.) with triethylamine.

The free radical bromination of *N*-acylglycinates of this type proceeds through the intermediacy of the general α-centred glycinyl radical (**34**) (**Figure 7**), produced by abstraction of an α-hydrogen atom by bromine atom. This radical is exemplary of the special class of "capto-dative"

radicals[35]. This term aptly describes the two substituent effects which combine to make this class of radicals especially stable.

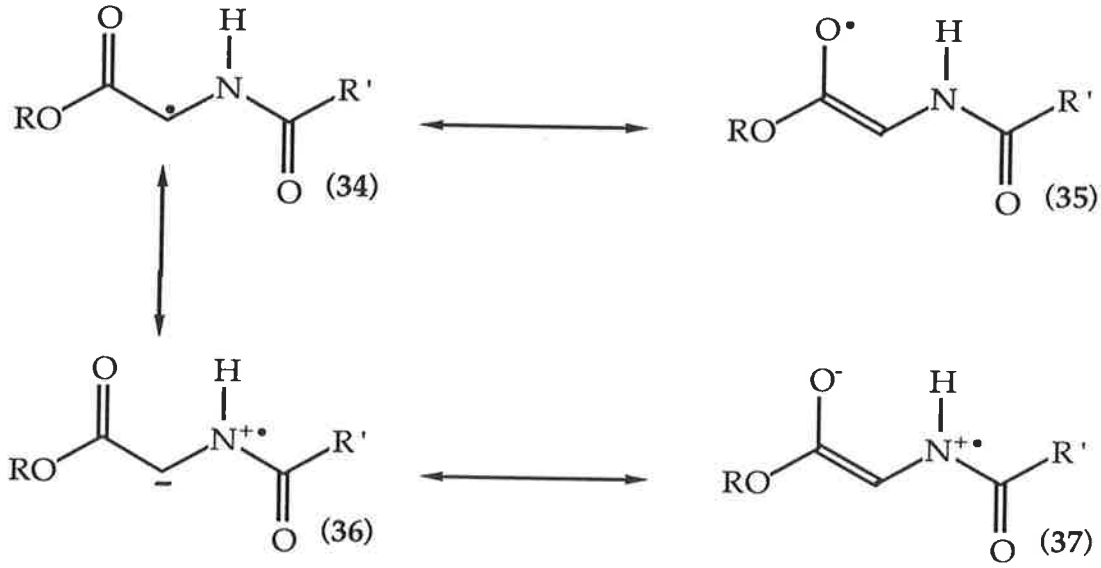


FIGURE 7

Stabilization of such glycinyl radicals results from the overlap of the semi-occupied p orbital with the π orbitals of the amido and alkoxycarbonyl substituents[35]. Specifically, the capto effect relates to delocalization of the unpaired electron into the electron withdrawing ester carbonyl group. The dative effect involves delocalization of a nitrogen lone pair electron into the semi-occupied p orbital. The resonance contributors involved in this effect are shown in **Figure 7**. Of course, for this type of delocalization to occur, all of the nuclei involved must be coplanar.

The net result of the capto-dative effect in this system is that glycinyl radicals are exceptionally stable and form very rapidly[36]. Synthetically, this has meant that elaboration of glycine moieties *via* free radical

bromination with *N*-bromosuccinimide has been, and continues to be, heavily exploited.

The choice of the nitrogen protecting group for this project is now restrained by two factors:-

1) It must be linked to nitrogen through an acyl group (in order to promote *C*-alkylation of the intermediate imino acetate, as previously discussed).

2) The protecting group must be compatible with the free radical bromination conditions to which the ester will be subjected.

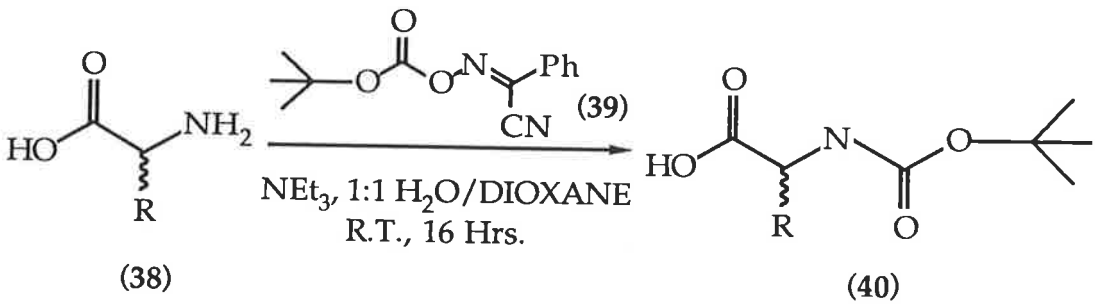
In addition, it must be readily removable in such a way that epimerization (leading to loss of optical purity) of the newly formed amino acid does not occur. The three common acyl linked nitrogen protecting groups are:-

1) Carbobenzyloxy: This is deemed unsuitable due to the benzyl group it contains, which could undergo competitive bromination by N.B.S.

2) Benzoyl: This is also deemed unsuitable due to the relatively forcing conditions required for its removal[37].

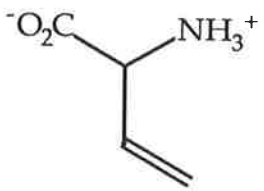
3) Tertiarybutyloxycarbonyl: (t-Boc) This is the protecting group which was chosen. The hydrogen atoms are all primary and unactivated (e.g. by adjacent heteroatoms and/or π systems). Hence, the methyl groups are highly unlikely to undergo radical substitution reactions. In addition, the *t*Boc group is cleanly and quickly removed by treatment with trifluoroacetic acid. It is easily introduced by treatment of free amino acids with 2-tert-butyloxycarbonyloxyimino-2-phenylacetonitrile (**39**), known as

"BOC-ON"[38] (**Scheme 6**). Futhermore, it is able to withstand catalytic hydrogenation, sodium in liquid ammonia, alkali and hydrazine[39].



SCHEME 6

It was intended that a variety of simple Grignard reagents would be added to the proposed intermediate 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate. The choice of appropriate Grignard reagents would result in the asymmetric synthesis of derivatives of some of the common, proteinogenic α-amino acids. The advantage of this is that it would initially make the determination of d.e. values much easier and less time-consuming.

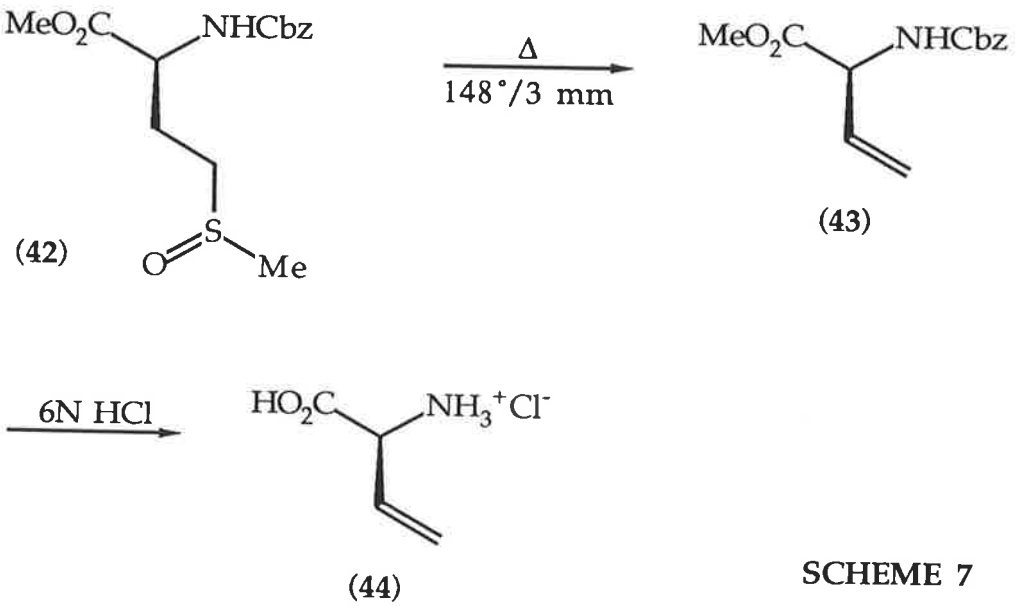


(41)

FIGURE 8

If the initial work proved successful, then Grignard reagents giving rise to non-proteinogenic α-amino acids would be studied. One possibility would be the use of vinylmagnesium bromide as the alkylating agent. This Grignard reagent should give rise to vinylglycine (**41**) (**Figure 8**), an α-amino acid not readily available (especially in optically pure form) and

of interest due to the antibiotic activity and enzyme inhibitory properties of β-γ-unsaturated amino acids[40,41]. A method to determine the d.e. of the vinylmagnesium bromide adduct would need to be devised, but may well evolve from the experience gained in the initial studies.



SCHEME 7

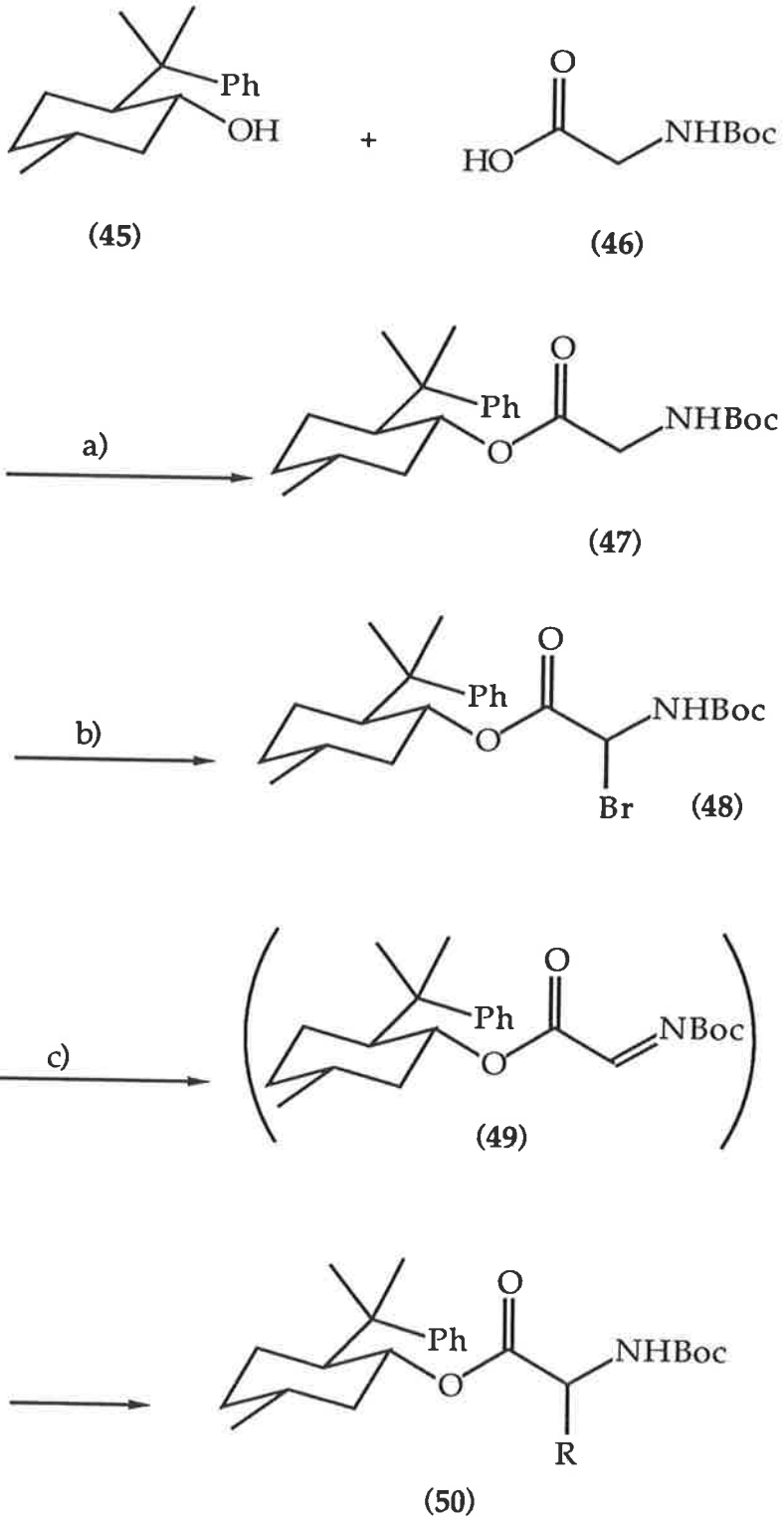
Optically pure (*S*)-vinylglycine has been synthesized by Rappoport and Afzali-Ardakani[42] through thermolysis of the optically active sulphoxide **(42)** (derived from (*S*)-methionine), followed by acid-catalyzed hydrolysis (**Scheme 7**). Other workers[43,44] have succesfully adopted conceptually similar approaches to the synthesis of optically pure vinylglycine involving oxidative elimination on (*S*)-glutamic acid derivatives. All of these cases, whilst providing vinylglycine in high enantiomeric purity, utilize natural amino acids in optically pure form. Hence, they are not true asymmetric syntheses, since no new chiral centres are formed. Furthermore, this approach allows for the synthesis of the parent, unsubstited vinylglycine only. The chemistry proposed here potentially allows for the general synthesis of substituted vinylglycines. At the time

this project was commenced, no true, general asymmetric synthesis of vinylglycines existed.

A further synthetic requirement is the facile coupling of (–)-8-phenylmenthol (**45**) and *N*-*t*-Boc-glycine (**46**) . This should be straightforward using the method of Hassner and Alexanian[45], involving the use of a catalytic amount of dimethylaminopyridine and a molar amount of dicyclohexylcarbodiimide. This technique effects esterification in high yields using mild conditions. Thus, the overall proposed synthetic route is as depicted in **Scheme 8**.

(–)-8-phenylmenthol is synthesized, by the chemistry depicted in (**Scheme 9**), from the relatively inexpensive monoterpene (*R*)-(+)-pulegone (**51**)[46], found in plants of the *labiatae* family. Copper (I) catalyzed conjugate addition of phenylmagnesium bromide to pulegone, followed by equilibration of the isomeric ketones (**52**) and (**53**), gives the two ketones in an 87:13 ratio. Dissolving metal reduction of the mixture of ketones gives the diastereomeric (1*R*, 2*S*, 5*R*) and (1*S*, 2*R*, 5*R*) alcohols, (**54**) and (**55**) respectively, also in an 87:13 ratio. Chromatographic purification gives the pure (1*R*, 2*S*, 5*R*) alcohol.

(–)-8-phenylmenthol's accessibility was at first somewhat restricted due to the tedious and logistically limiting necessity to purify it by chromatography. However, Ort[56] has reported an improved and more comprehensive synthesis resulting in (–)-8-phenylmenthol now being readily available. The key improvement made by Ort is the separation of the major *trans*-2,5 isomer of 8-phenylmenthol from its *cis* counterpart through fractional recrystallization of their chloroacetate esters (**Scheme 9**), eliminating the need for chromatography.

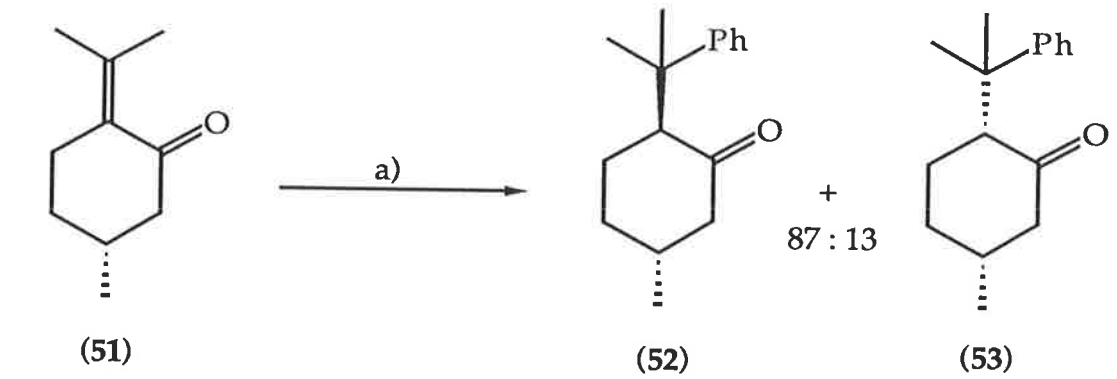


a) D.C.C., D.M.A.P., Et_2O, R.T.

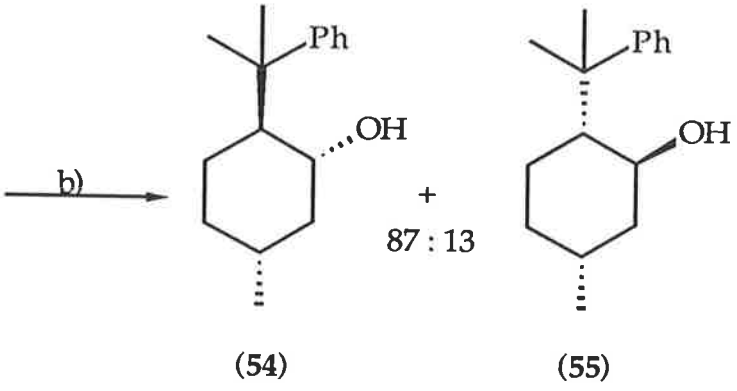
b) N.B.S., hν, Δ.

c) RMgX (2.2 eq.), Et_2O, -78°C, 2 hrs.

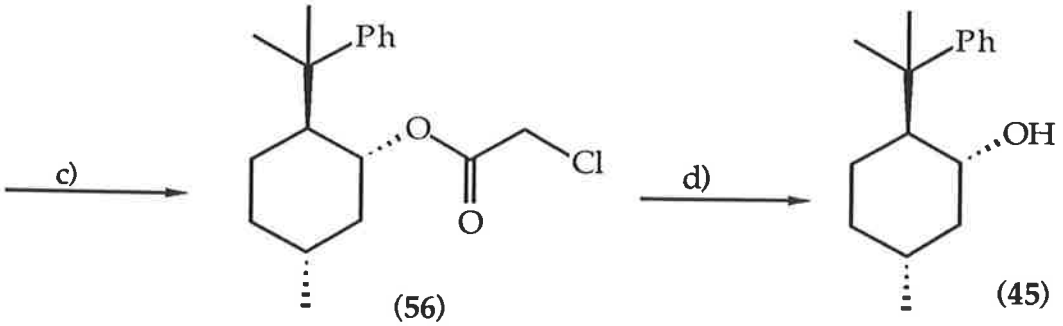
SCHEME 8



(51) (52) (53)



(54) (55)



(56) (45)

a) i) PhMgBr, CuBr, Et_2O, -20°C. ii) 2N HCl.
iii) KOH, Δ. b) Na, iPrOH, $PhCH_3$, Δ.
c) i) $ClCH_2COCl$, $PhNMe_2$, Et_2O, 0°C- Δ.
ii) 2X Fractional Recrystallization from EtOH.
d) KOH, EtOH, Δ.

SCHEME 9

(–)-8-phenylmenthol (45) is a chiral auxiliary first prepared, in both enantiomeric forms, by Corey [46,47] in 1975. Corey's team successfully incorporated an asymmetric Diels-Alder reaction of 8-phenylmenthol acrylate into their synthesis of an optically active prostaglandin intermediate[46]. It has since been successfully used in several types of asymmetric synthesis, including Diels-Alder reactions[48,49,50,51], Grignard additions[23,24,25], conjugate additions[52] and ene reactions[53,54,55]. As its name implies, 8-phenylmenthol is formally derived from menthol, with the hydrogen at C-8 being replaced by a phenyl group.

The basis of 8-phenylmenthol's power as a chiral auxiliary is the steric shielding exerted by the very large phenylmethylethyl group. Approach of reactants to prochiral moieties esterified to the 1-hydroxyl is possible from one side of the molecule only. In addition, there is a convincing evidence[57,58] which indicates that the phenyl ring of the 8-phenylmenthyl group participates in π-π interactions with the acid moiety. 8-phenylmenthyl glyoxylate exemplifies this phenomenon. Indications are that the π-π interaction which holds the prochiral glyoxylate moiety in close proximity to the phenyl ring is at least partly responsible for the *s-cis* configuration of the two carbonyl groups[57].

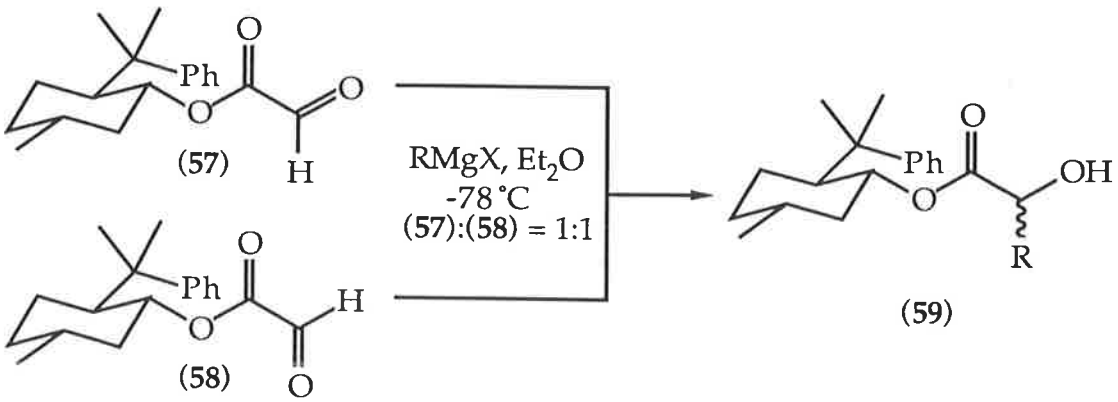


FIGURE 9

The latter effect is exemplary of an important aspect of asymmetric synthesis. The conformational rigidity of the prochiral moiety attached to a chiral auxiliary is as important a factor as the diastereofacial blocking power of the chiral auxiliary itself. This concept is illustrated by the hypothetical example depicted in **Figure 9**. If 8-phenylmenthyl glyoxylate were to exist as a 1:1 mixture of the *s-cis* (**57**) and *s-trans* (**58**) rotamers in ether solution prior to addition of a Grignard reagent, a 1:1 mixture of the 2-(*S*) and 2-(*R*) glycolates (**59**) would result even if the chiral auxiliary blocked the rear face with infinite efficiency.

The fact that 8-phenylmenthol imparts conformational rigidity on the glyoxylate moiety leads to the expectation that the analogous imine (**49**) will behave similarly. If so, the approach to asymmetric α-amino acid synthesis outlined here should be successful.

ANALYSIS OF STEREOISOMER RATIOS IN AN ASYMMETRIC SYNTHESIS

DIASTEREOMERIC EXCESS:

By virtue of the fact that diastereomers have differing ~~internal energies,~~ physical properties determination of d.e. values can be achieved, in principle, either by N.M.R., achiral* H.P.L.C. or achiral* G.C. analysis.

ENANTIOMERIC EXCESSES:

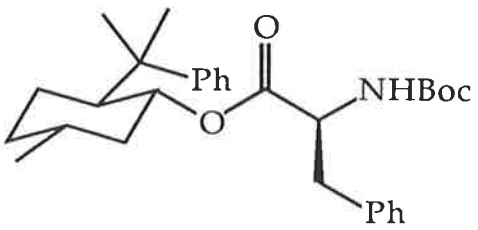
As enantiomers have the same ~~internal energies~~ physical properties, e.e. determination entails either

i) Conversion to diastereomers by treatment with ~~homochiral~~ enantiomerically pure derivatizing agents[59] followed by conventional diastereomer analysis, or

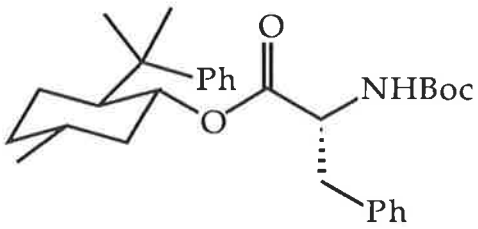
* Stationary phase

ii) Use of chiral shift reagents for N.M.R. analysis[60], or chiral H.P.L.C.[61] or G.C.[62] columns, all of which differentiate between enantiomers by virtue of diastereomeric interactions. between the enantiomers and the chiral reagent

As alluded to above, one of the advantages of using a covalently bound chiral auxiliary such as 8-phenylmenthol is that compounds which are epimeric at the newly formed chiral centre are, by necessity, diastereomeric. The subsequent chromatographic and spectoscopic differences between the two diastereomers means that determination of their relative proportions can often be determined directly by chromatographic or N.M.R. analysis. Thus conversion to diastereomers, chiral H.P.L.C. or G.C., or use of N.M.R. optical shift reagents is circumvented. The phenyl group in 8-phenylmenthol is, of course, detectable by U.V. spectroscopy (at 254 nm), a fact which makes H.P.L.C. analysis with U.V. detection a particularly attractive candidate for diastereomer analysis.



(60a)



(60b)

FIGURE 10

The diastereomeric phenylalanine derivatives (**60a**) and (**60b**) (**Figure 10**) are resolvable by T.L.C.[63]. Hence, it is expected that H.P.L.C. will serve as a means of establishing the diastereomeric purity of all of the diastereomeric α-amino acid derivatives of this kind produced during the course of this work. To this end, it is intended to synthesize a series of authentic

standards to form a basis for the analysis of the stereochemical composition of the Grignard adducts (**50**). Esterification of the *N*-*t*-Boc derivatives of commercially available racemic amino acids with 8-phenylmenthol will furnish 1:1 mixtures of diastereomers.

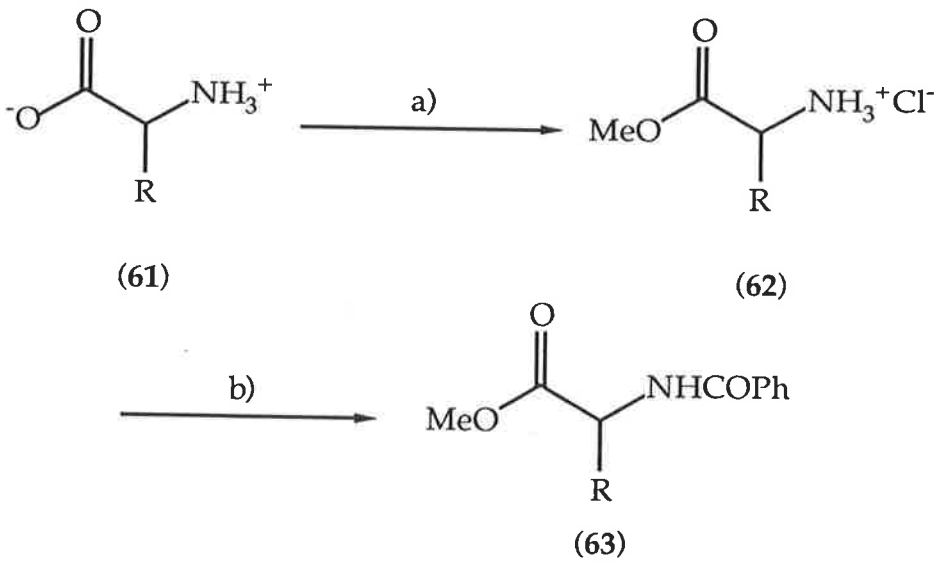
These diastereomeric mixtures will not only establish if the diastereomeric products of the Grignard additions are resolvable by H.P.L.C. (and ^{1}H and ^{13}C-N.M.R.), but will also prove the authenticity of the Grignard adducts through N.M.R. and H.P.L.C. correlation. Integration of the peaks due to each diasteromer will yield the required ratios. Thus synthesis of the diastereomeric mixture derived from the coupling of (*R*,*S*)-alanine with (–)-8-phenylmenthol will establish the degree of induction for the MeMgI addition to the bromide (**48**). Likewise, the mixture derived from (*R*,*S*)-valine will be used for correlation with the diastereomeric products of *i*-PrMgI addition, and so on. Alternatively, should the ^{1}H-N.M.R. spectra of the diastereomeric mixtures show distinct resonances for each isomer, integration of the areas of suitable signals (i.e. baseline resolved) could also be a means of calculating diastereomeric excesses.

The last synthetic requirement for this project's success is the hydrolysis of the Grignard adducts (**50**). In any asymmetric synthesis involving a covalently bonded chiral auxiliary, its facile removal is essential. Furthermore, this must be achieved without loss of optical purity (both in the desired product and the chiral auxiliary). In the case of the amino esters involved here, this entails employing conditions which will not enolize the amino acid moiety (i.e. remove α-protons).

Hydrolysis of peptides and proteins to optically pure amino acids is routinely carried out in refluxing 6N HCl. Hence, this method will

initially be applied to the hydrolysis of (**50**). Treatment of these *N*-*t*-Boc-amino acid 8-phenylmenthyl esters with neat trifluoroacetic acid generates the corresponding trifluoroacetate salts. Treatment of the salts with refluxing 6N HCl should effect their hydrolysis; whether the optical purity of the amino acid is undiminished remains to be seen.

To determine the optical purity of the amino acids produced, and hence whether hydrolysis proceeds with or without racemization, two analytical methods may be employed. The first is measurement of the specific rotation of the amino acids produced and comparison with literature values. The susceptibility of optical rotation readings to unsuspected impurities and minor variations in experimental conditions, however, may give erroneous results. Consequently, spectroscopic and chromatograpic methods have superceded this technique.



(**61**) (**62**) (**63**)

a) MeOH, HCl, R.T. b) PhCOCl, $KHCO_3$, EtOAc/ H_2O

SCHEME 10

Suitably derivatizing the amino acids for analysis with a chiral H.P.L.C. column capable of resolving the racemic pairs of these derivatives is considered a more reliable analytical technique. The *N*-benzoyl/methyl ester derivatives (**63**) will be used as analytical H.P.L.C. standards, as the racemic alanine derivative (**63**, R = Me) has been previously resolved[64] on a Pirkle[61] column. Means of synthesizing the derivatives are depicted in **Scheme 10**.

Chapter 1 - Results and Discussion

1.1 SYNTHESIS OF (–)-8-PHENYLMENTHOL AND ANALYTICAL STANDARDS

The preparation of (–)-8-phenylmenthol (**45**), described in Organic Syntheses[56] by Ort, makes this useful chiral auxiliary markedly more accessible. Due to the elimination of the need for chromatographic purification, the enantiomerically and diastereomerically pure alcohol can be produced in up to twenty gram amounts in one run (i.e., research laboratory scale) with relative ease.

Ort's method is superior to those previously published due to the key fractional recrystallization of the chloroacetate esters of alcohols (**54**) and (**55**) (Introduction, **Scheme 9**). This step proceeded smoothly, yielding the pure (1*R*, 2*S*, 5*R*) ester (**56**), as indicated by its sharp melting point (83-84°C, lit.[56] 82-83°C). Saponification of the ester proceeded almost quantitatively to give (–)-8-phenylmenthol.

The diastereomeric purity of the (–)-8-phenylmenthol produced in this way was determined by H.P.L.C analysis. During the course of earlier (–)-8-phenylmenthol syntheses, significant quantities of the (1*S*, 2*R*, 5*R*) isomer of (–)-8-phenylmenthol ("epient-8-phenylmenthol," (**64**)) were acquired. With a mixture of the two diastereomers in hand, it was possible to develop H.P.L.C. conditions which effected their resolution. Thus, it was found that isocratic elution with 9:1 hexane/ether fully resolved the two diastereomers (detected at 254nm). Under these conditions, the (–)-8-phenylmenthol produced by saponification of the recrystallized chloroacetate showed no trace of the unwanted (1*S*, 2*R*, 5*R*)

isomer. It is worth noting that this diastereomer is virtually the enantiomer of the (1*R*, 2*S*, 5*R*) diastereomer (save for the methyl group attached to C-5 being epimeric). This is evident upon inspection of the structure for **(65)** shown in **Figure 11**. Indeed, Whitesell[65] has shown that the sense of chirality it induces is opposite to that induced by (–)-8-phenylmenthol. Hence, if a mixture of the two diastereomers is used as the chiral auxiliary in an asymmetric reaction, the enantiomeric purity of the chiral product obtained after removal of the chiral auxiliary will be limited. It is therefore of vital importance that (–)-8-phenylmenthol used as a chiral auxiliary is diastereomerically and enantiomerically pure.

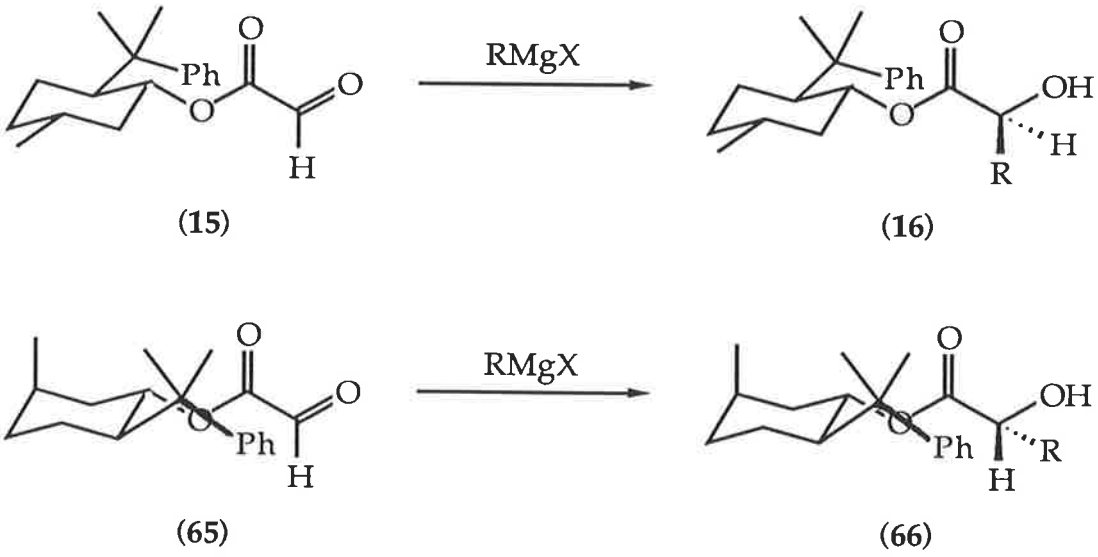


FIGURE 11

The enantiomeric purity of the (–)-8-phenylmenthol produced was determined by polarimetry. The rotation observed ($[\alpha]_D^{20} = -26.4° \pm 0.5°$) was in very close agreement with that reported by Ort[56] ($[\alpha]_D^{20} = -26.4° \pm 0.1°$), indicating that the alcohol was enantiomerically pure, within the limits of detection by polarimetry. The overall chemical yield of 39% achieved here (allowing for the fact that the starting pulegone

was 85%, technical grade) compares favourably with the reported yield[56] (24-37%).

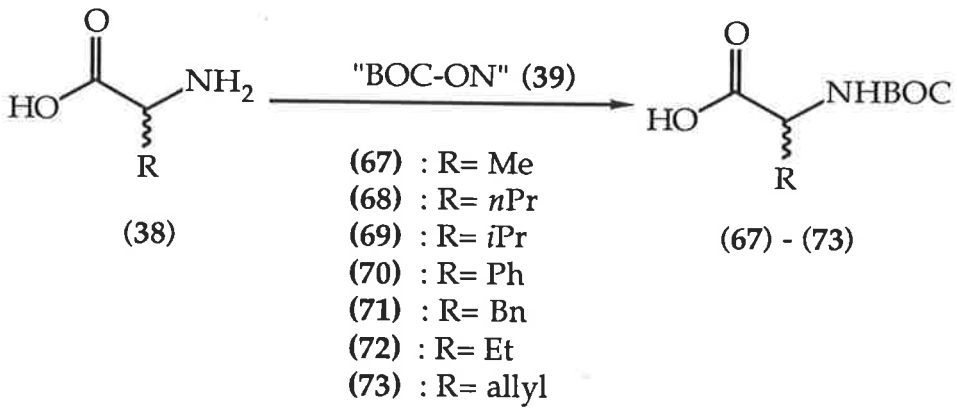
Coupling of (–)-8-phenylmenthol (**45**) with *N-t*-Boc-glycine (**46**) using the method of Hassner and Alexanian[45] proceeded smoothly to give the ester (**47**) in 93% yield after purification by "Dry Column" flash chromatography[66]. Column chromatography was the only effective means of purification of this compound, since it was a sticky, glassy substance which would not crystallize and distilled only at elevated temperatures under high vacuum. Almost without exception, all of the α-substituted 8-phenylmenthyl *N-t*-Boc-glycinates encountered during the course of this work also possessed these properties.

Proton and carbon N.M.R. analysis of (**47**) unambiguously confirmed the expected structure. Of particular interest were the signals due to the two diastereotopic α-protons. The pattern observed was typical of an AB quartet further coupled to a third, vicinal proton. Each α-proton resonated as a doublet of doublets. These two multiplets were centred at δ 3.05 and δ 3.29, with the magnitude of the geminal coupling being 15.1 Hz and vicinal coupling to the amide proton being 5.9 Hz and 5.3 Hz respectively. The amide proton signal was a broadened doublet of doublets centred at δ 4.38.

The broad-band decoupled ^{13}C-N.M.R. spectrum of this compound exhibited the expected nineteen signals. D.E.P.T. spectroscopy enabled the assignment of each resonance as having arisen from a primary, secondary, tertiary or quaternary carbon atom. This knowledge, combined with the use of ^{13}C-N.M.R. correlation tables[68], enabled the unambiguous assignment of every resonance. This proved to be of great benefit in the

interpretation of the ^{13}C-N.M.R. spectra of all of the α-substituted derivatives of this parent compound encountered during the course of this project.

Substitution at the α-position resulted in a *ca.* 7-16 p.p.m. downfield shift of the α-carbon resonance (situated at δ 42.26 in the case of the parent compound). The chemical shifts of the remaining peaks changed slightly, but these shifts were of sufficiently small magnitute to still allow for the unambiguous assignment of all peaks by comparison to the parent compound (**47**). Assignment of the peaks due to the α-substituent was easily achieved as these peaks usually possessed chemical shifts distinctly different to those of the basic carbon skeleton.



(38)

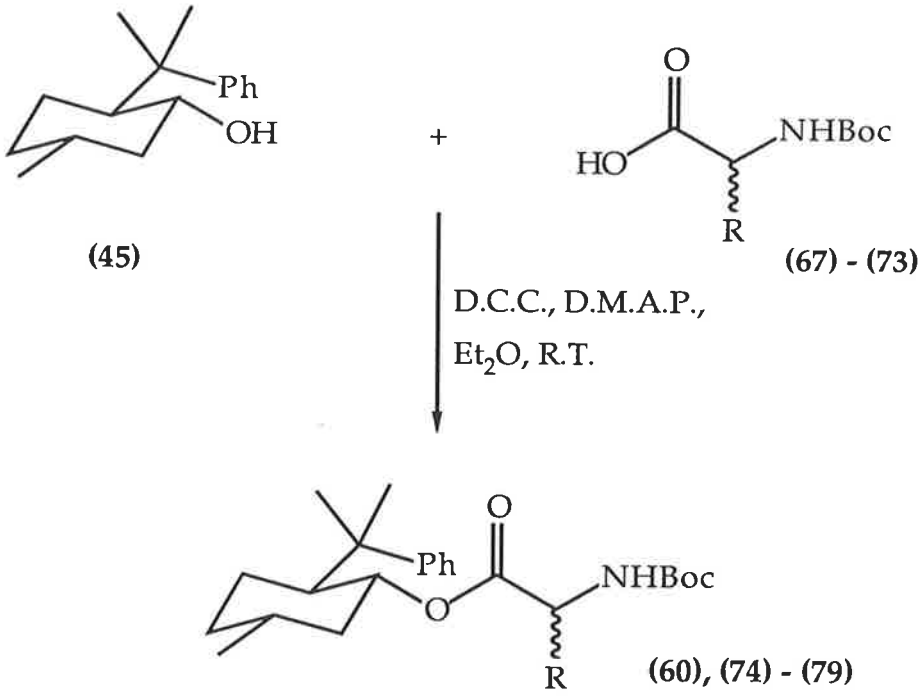
(67) : R= Me
(68) : R= *n*Pr
(69) : R= *i*Pr
(70) : R= Ph
(71) : R= Bn
(72) : R= Et
(73) : R= allyl

(67) - (73)

SCHEME 11

The synthesis of the *N-t*-Boc protected amino acids (**67**)-(**73**) following the technique of Itoh *et.al*[38] using "BOC-ON" (2-tertiarybutyloxycarbonyl oxyimino-2-phenylacetonitrile) (**39**) was both straightforward and high yielding (66-84%) (**Scheme 11**). The *N-t*-Boc amino acids produced were pure enough to use further without any purification.

Esterification of the racemic *N*-*t*-Boc amino acids (**67**) to (**73**) with (−)-8-phenylmenthol, also using Hassner and Alexanian's[45] method, proceeded smoothly (**Scheme 12**). The resultant equimolar mixtures of C-2 epimers were obtained in yields ranging from 76-96% after routine purification by flash chromatography[67]. These mixtures gave satisfactory elemental analyses.



(67) , **(74)** : R= Me
(68) , **(75)** : R= *n*Pr
(69) , **(76)** : R= *i*Pr
(70) , **(77)** : R= Ph
(71) , **(60)** : R= Bn
(72) , **(78)** : R= Et
(73) , **(79)** : R= allyl

SCHEME 12

All of the diastereomeric pairs (**60a,b**) and (**74a,b**)-(**79a,b**) resolved by T.L.C. on silica (4:1 hexane/ether). This meant that T.L.C. could be used as a qualitative means of ascertaining whether or not the relevant Grignard

additions had proceeded with asymmetric induction. This observation was also significant in that products derived from the asymmetric Grignard additions to the bromide (**48**) could be purified by column chromatography. From a preparative viewpoint, the diastereomerically pure samples thus obtained could then yield enantiomerically pure amino acids, regardless of the selectivity of the asymmetric step.

Subsequent H.P.L.C. analysis of the diastereomeric pairs (**60a,b**) and (**74a,b**)-(**79a,b**) showed that, in all cases, the two diastereomers separated to baseline resolution, under the same conditions. This involved isocratic elution utilizing 19 : 1 hexane/ethyl acetate as the mobile phase, with a flow rate of 2.0 ml/minute. The adsorbent was 10 μm normal phase silica. Under these conditions, elution times for all of the *N*-*t*-Boc-amino acid (–)-8-phenylmenthyl esters analyzed were less than ten minutes. A U.V. detector operating at 254 nm. was able to detect microgram quantities of material. This represented a very simple, rapid and sensitive analytical method which ultimately enabled the Grignard addition products (**50**) to be analyzed directly. Thus, determination of the diastereomeric excess of each Grignard addition reaction did not necessitate more complex and laborious analytical methods.

Small samples of each diasteremer within the epimeric mixtures (**60a,b**) and (**74a,b**)-(**79a,b**) were obtained by preparative H.P.L.C. F.A.B. mass spectroscopic analysis of these diastereomerically pure samples confirmed that, in each case, the two components within each mixture of diastereomers possessed the same molecular weight. The observed molecular weights were, in each case, equal to those calculated.

The ^{1}H-N.M.R. spectra of all, and ^{13}C-N.M.R. spectra of some of the diastereomerically pure compounds were obtained. In all cases, the spectra were consistent with the expected structures. For each diastereomeric pair, the 2-(*S*) and 2-(*R*) diastereomers were clearly differentiable by ^{1}H and ^{13}C-N.M.R. (300 Mz, 75.5 MHz respectively). In particular, the chemical shift difference between the ring methyl (A), *gem*.-dimethyl (B) and (C), tertiarybutyl (D), α (E) and alkoxy ester (F) (**Figure 12**) proton resonances was of sufficient magnitude to allow for a crude estimate of diastereomeric excess. Similarly, most of the ^{13}C-N.M.R. resonances of a given diastereomer were distinguishable from the complementary resonances of its C-2 epimer. The alkoxy ester carbon (G), ring methyl (H) and quaternary tertiarybutyl carbon (I) (**Figure 12**) were particularly diagnostic. Thus N.M.R. proved to be a valuable tool as a "first-glance" qualitative means of assessing the stereochemical outcome of the Grignard alkylation reactions.

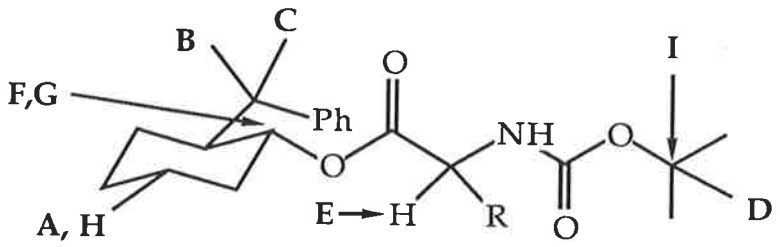


FIGURE 12

The ^{1}H-N.M.R. spectrum of 8-phenylmenthyl (*R*)-*N*-*t*-Boc-phenylglycinate (**77b**) revealed an interesting and unusual feature of this molecule. The two diastereotopic geminal methyl groups of the 8-phenylmenthyl moiety resonated at unexpectedly low field (δ 0.80 and δ 1.00) when compared to the other 2-(*R*) epimers in this series. The chemical shifts of the two geminal methyl groups in these compounds are typically within the

narrow ranges of δ 1.23-1.25 and δ 1.31-1.33. Furthermore, for (**77b**), the chemical shift difference between these two signals is 0.20 p.p.m., substantially larger than the typical value of 0.08-0.10 p.p.m. These effects are presumably due to the molecule adopting a conformation in deuteriochloroform solution where the α-phenyl group of the α-amino acid moiety exerts magnetic shielding effects of different magnitudes on these two sets of methyl protons. No such effect is seen in the case of the 2-(*S*) diastereomer (**77a**), whose geminal methyl groups have typical proton chemical shifts of δ 1.22 andδ 1.32. This strongly infers that the α-phenyl group of the 2-(*S*) diastereomer points away from the 8-phenylmenthyl phenyl group, and that the opposite is true in the case of the 2-(*R*) diastereomer.

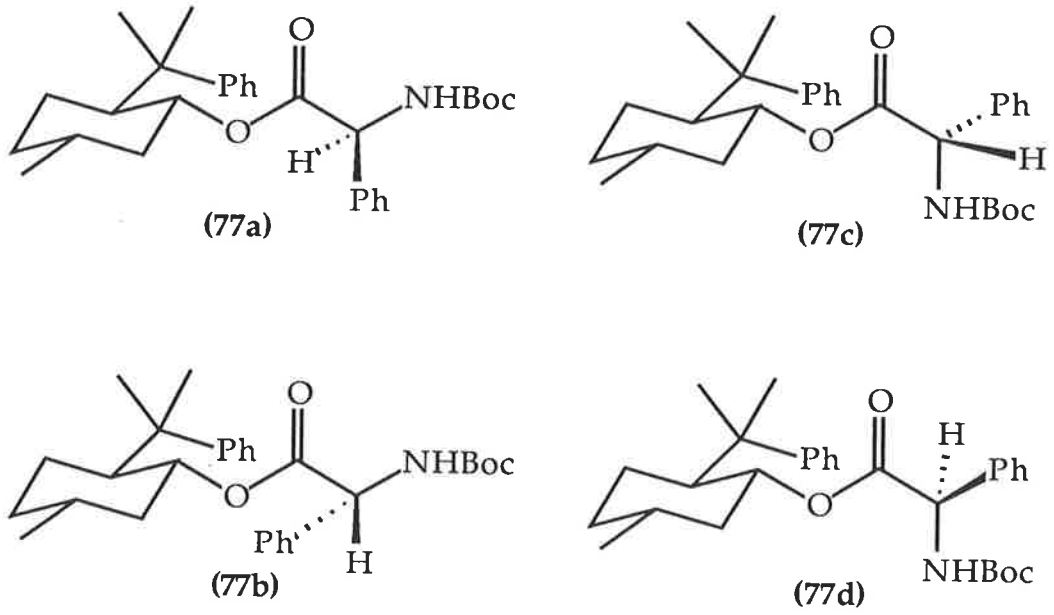


FIGURE 13

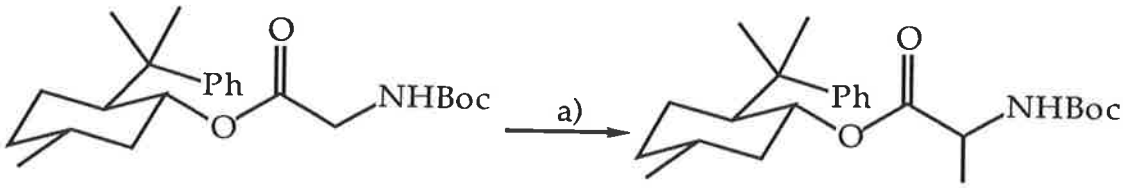
These effects can only be rationalized by the assumption that the amino acid moiety of both diastereomers adopts the *Z* conformations (**77a**) and (**77b**) shown in **Figure 13**. If the *E* rotamers (**77c**) and (**77d**) prevailed in both cases, one would expect the opposite anisotropic effects to occur, since

the 2-(*S*) isomer would then have the α-phenyl group pointing towards the phenyl group of the 8-phenylmenthyl moiety. By extension, it is very probable that all of the *N*-*t*-Boc-amino acid 8-phenylmenthyl esters (**60a,b**) and (**74a,b**)-(**79a,b**) adopt the *Z* conformation.

Re-examination of the ^{1}H-N.M.R. spectrum of the 2-(*R*)-phenylalaninate (**60b**) revealed that the same effect did not occur. That is, the chemical shifts of the geminal methyl group protons (δ 1.18 and δ 1.27) were only slightly upfield of the "normal" ranges for these nuclei. The absence in this case of an anisotropic effect of the same magnitude as that displayed by the 2-(*R*)-phenylglycinate (**77b**) can be rationalized by appreciation of the greater conformational freedom of the benzyl group of (**60b**) relative to the phenyl group of (**77b**). Due to the presence of the intervening benzylic methylene group, the β-phenyl group of (**60b**) could forseeably minimize steric interactions with the 8-phenylmenthyl moiety by rotation about the α-β carbon-carbon bond. This in turn would explain the absence of magnetic shielding of the geminal methyl groups of this compound, as evidenced by their typical proton chemical shift values.

1.2 GRIGNARD ADDITION TO 8-PHENYLMENTHYL *N*-*t*-BOC-2-BROMOGLYCINATE (48)

The bromination of 8-phenylmenthyl *N*-*t*-Boc-glycinate (47) with freshly recrystallized *N*-bromosuccinimide under ultraviolet light photolysis in dry carbon tetrachloride proceeded rapidly (ten minutes) to afford the bromide (48) as a colourless oil, in virtually quantitative yield (**Scheme 13**). The bromide later solidified to an off-white, amorphous solid upon standing under nitrogen. Completeness of reaction and high purity were indicated by ^{1}H-N.M.R., as judged by the complete absence of the α-proton signals of starting material and the appearance of a doublet at δ 4.88 attributed to the α-proton of the product (48). Care needed to be exercised in handling the bromide (48) as it was sensitive to moisture (due to elimination of hydrogen bromide). Generally, the bromide was used within thirty minutes of its preparation in order to avoid any decomposition, though it was stable for up to a week when stored under dry nitrogen in a refrigerator at 5°C.



(47) (48)

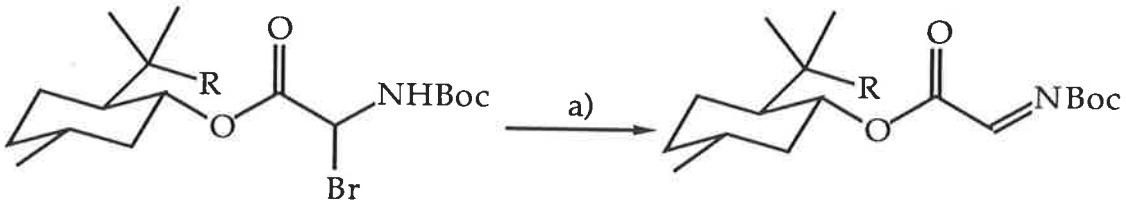
a) N.B.S. (1.01 equivalents), CCl_4, hν, Δ, 10 minutes.

SCHEME 13

A very interesting result concerning this α-bromoester is that it is almost certainly produced as one diastereomer. That is, the radical bromination proceeds with high diastereoselectivity. This conclusion was initially based on the 300 MHz ^{1}H-N.M.R. spectrum of (48). Quite clearly, only one

resonance for each type of proton was present. This is convincing evidence in light of the ^{1}H-N.M.R. spectra of the diastereomeric mixtures (**60a,b**) and (**74a,b**)-(**79a,b**), which exhibited dual resonances for many protons. This ^{1}H-N.M.R. evidence, and other evidence for the diastereomeric purity of the bromide (**48**), will be discussed at a later, more appropriate stage in this thesis.

This high asymmetric induction in the bromination of (**47**), though not important for the Grignard additions as the α-carbon loses its chirality upon elimination of hydrogen bromide, is an exciting result since the reaction occurs at a relatively high temperature (77°C) compared to most asymmetric induction reactions, which are generally performed at low temperatures. In addition, very few examples of asymmetric induction at radical centres in acyclic systems are known. Again, this aspect will be discussed in considerably more depth in a later section.



R = Ph: (**48**)
R = H: (**81**)

a) NEt_3, Et_2O, 0°C - R.T.

R = Ph: (**49**)
R = H: (**82**)

SCHEME 14

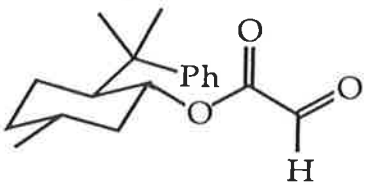
It was found that the imine (**49**), the proposed intermediate of Grignard addition to the bromide (**48**), could be generated by treatment of (**48**) in anhydrous ether with one equivalent of triethylamine (**Scheme 14**). The imine of the menthyl analogue (**82**) was produced from bromide (**81**) in a similar manner (**Scheme 14**). The bromide (**81**) was produced by

bromination of *N*-*t*-Boc-glycine (–)-menthyl ester (**80**). The imines (**49**) and (**82**) were insufficiently stable for full characterization, but the ^{1}H-N.M.R. spectral data of the two compounds were consistent with their structures. With ^{1}H-N.M.R. data now in hand for (**47**), its bromide (**48**) and its imine (**49**), along with their respective menthyl analogues (**80**), (**81**) and (**82**), some interesting and encouraging points were observed. The relevant data are summarized in **Table 1.**

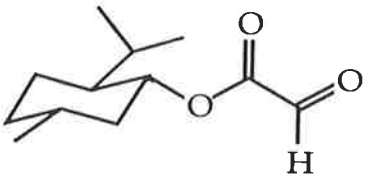
AUXILIARY	α PROTON CHEMICAL SHIFT (δ)		
	PARENT (No.)	BROMIDE (No)	IMINE (No.)
MENTHOL	3.89 (**80**)	6.22 (**81**)	7.73 (**82**)
8-Ph-MENTHOL	3.17 (**47**)	4.88 (**48**)	6.70 (**49**)

TABLE 1

Clearly, all of the α-proton chemical shifts for the 8-phenylmenthyl series are substantially lower than those for the menthyl series. Molecular models indicate that compounds (**47**), (**48**) and (**49**) can readily adopt a conformation in which the α-carbon atom of these 8-phenylmenthyl esters is situated directly over the middle of the phenyl group. Hence, it is reasonable to assume that significant magnetic shielding of the α-carbon by the induced magnetic field of the phenyl group is responsible for this anisotropic effect.



(15)
α-H: δ 8.50



(83)
α-H: δ 9.30

FIGURE 14

Work by Whitesell's group[58] at Austin supports this assumption. These workers observed that the chemical shift of the glyoxylate proton of 8-phenylmenthyl glyoxylate (**15**) was 0.80 p.p.m. upfield of that of the menthyl analogue (**83**) (**Figure 14**). This work was part of a comparitive study of the efficiencies of several chiral auxiliaries analogous to 8-phenylmenthol. In this study, Whitesell observed that the chemical shifts of protons at the α-position of acid moieties esterified to these 8-phenylmenthol analogues were shifted downfield (relative to the corresponding menthyl esters) to different extents. Furthermore, a rough correlation was observed between the magnitude of the upfield shift of the α-proton signal and the amount of asymmetric induction afforded by the chiral auxiliary concerned. As the iminoacetate (**49**) is the actual species to which Grignard reagents would add, the 1.03 p.p.m. downfield shift of the α-proton of this species relative to the menthyl analogue (**82**) was most encouraging. In light of Whitesell's findings, this large chemical shift difference suggested that the iminoacetate (**49**) would undergo highly diastereoselective alkylation by Grignard reagents.

The Grignard reagents used in the alkylation studies described here were synthesized from the appropriate alkyl halide in ether under standard conditions (the only exception being vinylmagnesium bromide in T.H.F.,

which was purchased from Aldrich Chemical Co.) and were stored under nitrogen in bottles equipped with rubber septa. They were standardized by hydrolysis of a 1.00 ml aliquot in 20.0 ml of 0.1000 M HCl followed by back titration of the excess acid with 0.1000 M NaOH.

Based on the concentrations determined by this method, a calculated volume of Grignard reagent (2.2 equivalents) was added dropwise to an efficiently stirred ethereal solution of the bromide (**48**), cooled to –78 °C. The only exception to this was the vinylmagnesium bromide addition, which was performed in T.H.F. Upon completion of Grignard reagent addition, the resultant mixture was stirred at –78 °C for two hours. At this time, the cold bath was removed and the mixture allowed to equilibrate to room temperature. Excess saturated ammonium chloride solution was then added to quench the reaction. Chromatographic purification was necessary in all cases in order to remove low R_f impurities. Care was taken to avoid fractionation of the two diastereomers produced. By this procedure, products (**84**)-(**91**) were obtained in widely varying yields of 51-84% (**Table 2**). The lower yields were for the isopropyl magnesium bromide addition (Entry 3, 51%) and vinylmagnesium bromide addition (Entry 7, 52%). Several attempts to improve these yields were unsuccessful.

For all of the Grignard addition products, T.L.C. and ^1H and ^{13}C-N.M.R. analysis indicated that exclusive *C*-alkylation had occured. Furthermore, comparison with the diastereomeric pairs (**60a,b**) and (**74a,b**)-(**79a,b**) revealed that, in most cases, mainly one diastereomer had been formed, indicating that high asymmetric induction had occurred. Compounds (**90**) and (**91**), however, (the products of vinylmagnesium bromide and

allylmagnesium bromide addition to the bromide (48)) showed some signs of a second diastereomer by both T.L.C. and ^{1}H -N.M.R. analysis.

ENTRY	R	No.	YIELD (%)	D. E. (%)
1	Me	(84)	72	98 [a]
2	*n*-Pr	(85)	84	95
3	*i*-Pr	(86)	51	98 [a]
4	Ph	(87)	82	90 [b]
5	Bn	(88)	58	90 [b]
6	Et	(89)	82	95
7	vinyl	(90)	52	52
8	allyl	(91)	67	57

All reactions in diethylether at -78°C except for entry 7 (Tetrahydrofuran, -20°C).

a) 2-(*R*) diastereomer not detected by H.P.L.C.

b) Accurate determination not possible by H.P.L.C.; estimate based on ^{1}H-N.M.R. and ^{13}C-N.M.R., which did not detect the 2-(*R*) diastereomer.

TABLE 2

H.P.L.C. analysis, however, was necessary for an accurate, quantitative determination of the diastereomeric excess values. Adduct (90) (vinylglycine addition) was analyzed by a different method that will be described later. Analysis of the Grignard adducts by H.P.L.C. was straightforward in all cases except for compounds (88) and (87), the products of benzylmagnesium bromide and phenylmagnesium bromide addition, respectively. These samples were contaminated by minor impurities which had very similar retention times to the minor, 2-(*R*) diastereomers, preventing accurate integration of the peaks due to these

diastereomers. Thus, the values for the d.e. of these samples quoted in **Table 2** are nominally 90%, since ^{1}H- and ^{13}C-N.M.R. failed to detect the minor, 2-(*R*) diastereomer.

The chemical and optical yields for the Grignard addition reactions carried out in this study are presented in **Table 2.** Overall, these results show that this approach to asymmetric α-amino acid synthesis was promising in so far as the asymmetric step proceeded with high diastereoselectivity, and in acceptable yield.

The reason for the reduced stereoselectivity in the cases of the vinylglycine (**90**) and allylglycine (**91**) syntheses may be that the Grignard reagents used (vinylmagnesium bromide and allylmagnesium bromide respectively) aggregate to a different extent than the other Grignard reagents used. Whitesell[23] found that the degree of aggregation of methylliithium profoundly influenced the diastereoselectivity of its addition reaction with 8-phenylmenthyl glyoxylate (**15**). When methyllithium alone was added to the glyoxylate in ether, no asymmetric induction at all was observed. The inclusion of lithium perchlorate, however, resulted in a diastereomeric excess of 60%.

It has been shown that Grignard reagents prepared from alkyl bromides and iodides are monomeric in T.H.F. solution[69,70]. Hence, the low diastereoselectivity (relative to the Grignard reagents prepared in ether) of the vinylmagnesium bromide addition to the α-bromoester (**48**), (which was conducted in T.H.F.) may be accounted for in light of Whitesell's findings described above. Alkylmagnesium halides are known to be aggregates in ether[69,70]. The larger effective size of the incoming nucleophile in these cases may result in enhanced facial selectivity in

addition to the imino group. Conversely, the small, monomeric vinylmagnesium bromide would be a less face-selective alkylating agent. Whether the same effect is responsible for the low diastereoselectivity of the corresponding allylmagnesium bromide addition is not so certain, as this reaction was performed in ether, which would be expected to cause aggregation of the allylmagnesium bromide. Although the aggregation argument is a plausible explanation in this case, it nevertheless remains as speculation.

^{1}H-N.M.R., T.L.C. and H.P.L.C. correlation with the authentic *N*-*t*-Boc-(*S*)-alanine, *N*-*t*-Boc-(*S*)-norvaline and *N*-*t*-Boc-(*S*)-valine 8-phenylmenthyl esters (**74a**), (**75a**) and (**76a**), synthesized from (*S*)-alanine, (*S*)-norvaline and (*S*)-valine respectively, confirmed that the major diastereomers of (**84**), (**85**) and (**86**) (produced in the relevant Grignard addition reactions) had the (*S*) configuration at the α-carbon. Coincidentally, this configuration is that of the majority of natural α-amino acids. Interestingly, in all three cases, the 2-(*S*) diastereomer was the first-eluting diastereomer. In addition, the α-proton of the 2-(*S*) diastereomer resonated at substantially lower field than the α-proton of its 2-(*R*) counterpart. The C-2 configuration of the major diastereomer produced in the remaining Grignard addition reactions was not confirmed by correlation with the corresponding authentic 2-(*S*) derivatives. However, the precedent established by these two cases allows for the assignment of the absolute configuration of the major diastereomer as 2-(*S*) in all cases.

These assignments were possible since, in addition to being the first-eluting diastereomer, the major diastereomer produced in all of the remaining Grignard addition reactions exhibited the same ^{1}H-N.M.R.

spectral characteristic. That is, the chemical shift of the α-proton of the major diastereomer was lower than the α-proton chemical shift of the minor diastereomer. **Table 3** , which compares the α-proton chemical shifts of the first and second eluting diastereomers for the epimeric mixtures (**60a,b**) and (**74a,b**)-(**79a,b**), clearly shows this.

ENTRY	R	No.	$\delta_{\alpha-H}$ (ppm)		Δδ (ppm)
			2-(*S*)	2-(*R*)	
1	Me	(74)	3.65	3.96	0.31
2	*n*-Pr	(75)	3.64	3.97	0.37
3	*i*-Pr	(76)	3.53	4.07	0.54
4	Ph	(77)	4.34	5.13	0.79
5	Bn	(60)	3.87	4.04	0.17
6	Et	(78)	3.57	3.93	0.36
7	vinyl	(90)	4.07	4.54	0.53
8	allyl	(79)	3.64	3.98	0.34

TABLE 3

The difference between the chemical shifts of the α-protons of the 2-(*S*) and 2-(*R*) diastereomers is almost certainly due to the magnetic shielding effect exerted by the phenyl group of the 8-phenylmenthyl moiety. As previously stated, the α-carbon of acid moieties esterified to 8-phenylmenthol is situated directly over the C-8'aromatic ring. The resultant downfield shift of α-protons in such esters has been observed by Whitesell[58]. **Figure 15** shows the general 2-(*S*) and 2-(*R*) 2-substituted glycinates (**92a**) and (**92b**). When drawn in these confomations, the α-proton of the 2-(*S*) epimer points toward the π-cloud of the phenyl ring,

whilst the α-proton of the 2-(*R*) epimer points away. Thus, the former proton experiences a greater magnetic shielding than the latter. Hence, the α-proton of the 2-(*S*) epimer resonates at significantly lower field than its 2-(*R*) counterpart.

(92a) (92b)

FIGURE 15

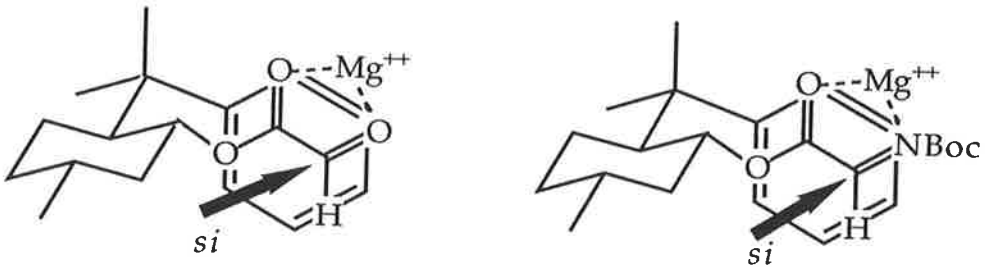
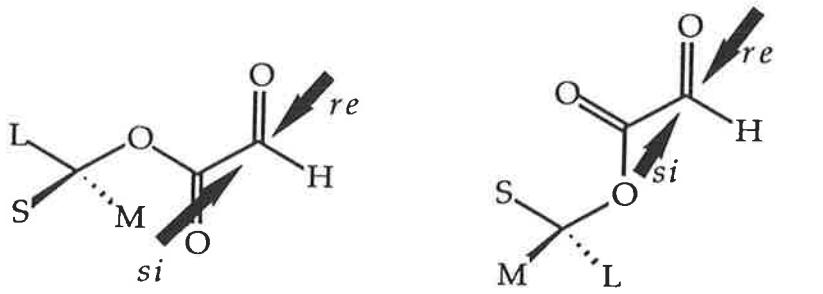


FIGURE 16

In an effort to rationalize the 2-(*S*) stereochemistry of the Grignard adducts (**84**)-(**91**), Whitesell's work on the glyoxylate ester of (–)-8-phenylmenthol (**15**)[23,24,25] was studied in greater depth. As discussed previously, Whitesell showed that the addition of Grignard reagents to the ester at –78°C in ether produced the 2-(*S*)-glycolates (**16**) (**Scheme 1**, Introduction) with very high (>98%) diastereomeric excesses. Whitesell rationalized this stereochemical outcome with the model shown in **Figure 16**. Steric shielding of the *rectus* face of the aldehyde carbonyl by the phenyl group results in the *sinister* face being selectively attacked by Grignard reagents.

Whitesell argued that the ester and aldehyde carbonyls were held in a *syn* arrangement by coordination with magnesium ion. If the presumption is made that the imine (**49**) is behaving analogously to the glyoxylate (**15**) (i.e., ester carbonyl and imino group held *syn* by magnesium ion, as in **Figure 16**), the selective formation of the 2-(*S*) isomers upon addition of Grignard reagents to the bromide (**48**) is accounted for.



PRELOG'S RULE WHITESELL'S MODEL

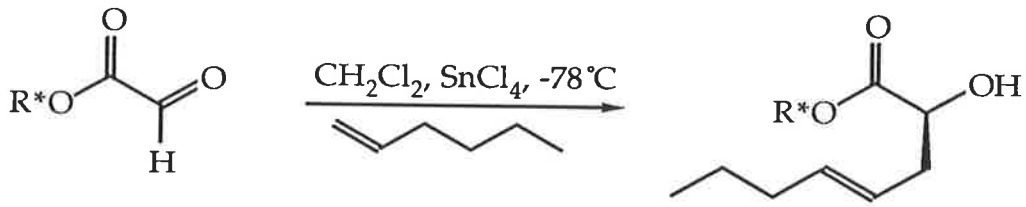
FIGURE 17

In a subsequent paper[24] Whitesell explained this model in greater detail. To rationalize the 2-(*S*) stereochemistry, a model which differed from Prelog's Rule[71,72] was invoked. As shown in **Figure 17**, Prelog's rule has the ester and aldehyde carbonyls disposed in an *anti* fashion, with the large group of the alcohol moiety *anti* to the ester carbonyl. Reagents will approach the aldehyde carbonyl from the side of the small rather than medium group due to steric constraints. In Whitesell's model, the two carbonyl groups are held *syn*, with the small group of the alcohol moiety *syn* to the ester carbonyl. Here, reagents approach from the side of the medium rather than the large group, again due to steric constraints.

It should be noted that both models predict the 2-(*S*) stereochemistry. Whitesell argues, with good cause, that his model has more merit in this

system as its basis of differentiation between the two prochiral faces of the glyoxylate ester is the difference in size between the medium and large groups. This accounts for the marked increase in stereoselectivity in progressing from menthol to 8-phenylmenthol, as the large group is changed from isopropyl to the huge phenylmethylethyl. Prelog's model states that the size difference between the small and medium groups is responsible for diastereofacial selectivity in these systems. As this size difference is not altered in changing from (–)-menthol to (–)-8-phenylmenthol (small = H, medium = CH_2 for both), the Prelog model fails to predict the superior diastereoselectivity of the latter chiral auxiliary. Furthermore, X-ray studies[73] indicate that the conformation proposed by Whitesell (with respect to the ester carbonyl and the C-1' ester hydrogen adopting the *syn* arrangement) is predominant, albeit in the solid state.

In order to account for the high diasteroeselectivity of Grignard addition to the imine (**49**), it is also necessary to discuss Whitesell's investigations into the reasons for the extremely high levels of asymmetric induction afforded by (–)-8-phenylmenthol. Whitesell's group[58] approached this problem by systematically modifying some of the structural elements of (–)-8-phenylmenthol. The relative efficiencies of these modified auxiliary alcohols were evaluated by comparing the asymmetric induction in the ene reaction of their glyoxylate esters (**93**) with 1-hexene, catalyzed by tin tetrachloride (**Scheme 15**).



(95) (96)

SCHEME 15

As a result of this study, Whitesell concluded that it is not the size alone of the phenyl group, but also its aromaticity, that are responsible for high asymmetric induction. He speculated that the phenyl group is intimately involved with the glyoxylate moiety (possibly through π-π interaction) in the transition state of the ene reaction. This leads to almost complete elimination of approach to the *rectus* face of the glyoxylate system. Oppolzer[50] put forward a similar argument to rationalize the high levels of asymmetric induction observed in the Diels-Alder reaction of 8-phenylmenthyl acrylate.

FAVOURABLE INTERACTION UNFAVOURABLE INTERACTION

FIGURE 18

In an earlier publication[57], Whitesell investigated the "π-π stacking" phenomenon exhibited by 8-phenylmenthyl glyoxylate. Firstly, in a theoretical approach, the glyoxylate moiety was approximated as 1,4-butadiene and the phenyl ring as benzene. Shown in **Figure 18** is the favourable nodal interaction between the Ψ_3 H.O.M.O. of benzene and the

Ψ_3 L.U.M.O. of ~~butadiene~~ the glyoxylate (when the carbonyls have a *cis* orientation) and the unfavourable interaction for the *trans* orientation.

In the same paper, photophysical experiments indicated that fluorescence quenching of the excited aryl fluorophore by the dicarbonyl occurs. That is, upon excitation of the phenyl chromophore at the appropriate wavelength (285 nm), the energy of the excited electron is not released by the normal fluorescence mechanism but instead excites the dicarbonyl system. For this to occur, the two chromophores must be in very close proximity; closer, in fact, than steric constraints would permit. The H.O.M.O. - L.U.M.O. interaction described above is the most likely explanation for the close proximity of the phenyl and dicarbonyl moieties.

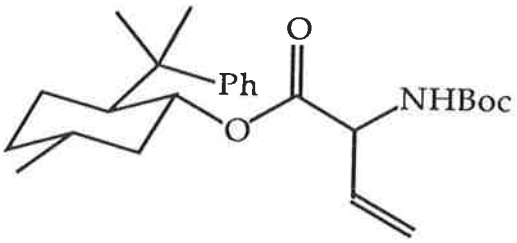
Combination of these two approaches neatly explains both the preference for the *cis* orientation of the carbonyls, and the remarkably efficient face selectivity in asymmetric reactions involving the glyoxylate ester (**15**). By analogy, the high *si* face selectivity observed in our study on Grignard reagent addition to the related iminoacetate (**49**) may also arise due to similar behaviour by this compound. That is, a similar π-π interaction between the planar, conjugated π system of the iminoacetate moiety and the π system of the phenyl ring of the 8-phenylmenthyl moiety leads to almost complete elimination of approach to the *re* face of the α-carbon of (**49**).

1.3 ANALYSIS OF VINYLMAGNESIUM BROMIDE ADDUCT (90).

The synthesis of the vinylglcine derivative (**90**) was unique in that this compound, unlike the adducts (**84**)-(**89**) and (**91**), which were derivatives of common α-aminoacids, was the derivative of a non-proteinogenic α-amino acid. Consequently, the chemistry involved in its synthesis, the means of establishing the diastereomeric ratio, and the assignment of the the absolute configuration of the two diastereomers produced, will be discussed in more detail.

The α-bromoglycinate (**48**), in T.H.F. solution at –20°C, was treated with two equivalents of a 1.0 M solution of vinylmagnesium bromide in T.H.F. in the usual way. This temperature differed from that employed in the other Grignard addition reactions (–78°C) as it was found that better chemical yields of (**90**) were obtained at –20°C, while the ~~optical yield~~ diastereoselectivity was unaltered. After two hours at this temperature, the homogeneous mixture was quenched with saturated ammonium chloride solution. T.L.C. analysis of the crude product revealed the presence of two spots at high R_f and a large low R_f streak. Purification by flash chromatography isolated the high R_f products in a combined yield of 52%. H.P.L.C. analysis of this material indicated that two products formed in *ca.* 76 : 24 ratio were present. These were separated by H.P.L.C. and each product analyzed by high-field N.M.R.

The first-eluting, major component (**90a**) gave a ^1H -N.M.R. spectrum consistent with the structure of (**90**) (**Figure 19**), the expected product of vinylmagnesium addition to the α-bromoglycinate (**48**). Besides the familiar features due to the 8-phenylmenthyl moiety, the spectrum contained an intense singlet at δ 1.47 attributed to the tertiarybutyl methyl



(90)

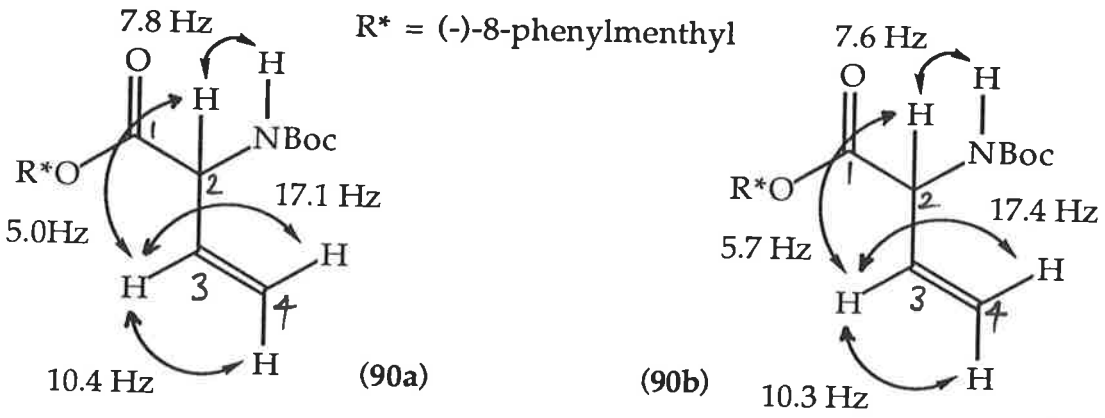


FIGURE 19

protons. A severely broadened multiplet due to the α-proton was centred at δ 4.07. The amide doublet appeared at δ 4.70 (J=7.8 Hz). In the vinylic region of the spectrum, two overlapping doublets, integrating for a total of two protons, were centred at δ 5.11 and δ 5.12, displaying coupling constants of 10.4 Hz and 17.1 Hz respectively. These resonances were attributed to the terminal vinylic protons of (**90**). The magnitude of the coupling constants indicated that the lower field doublet was due to the proton *cis* to the vicinal C-3 vinylic proton, whilst the higher field doublet was due to the proton *trans* to the C-3 proton. A doublet of doublets of doublets integrating for one proton appearing at δ 5.59, with J=5.0, 10.4 and 17.1 Hz, was assigned to the C-3 vinylic proton. The eight line pattern is accounted for by considering that this proton is coupled to both terminal vinylic protons (10.4 Hz *cis* coupling and 17.1 Hz *trans* coupling) as well as the vicinal α-proton (5.0 Hz coupling). The reciprocal 5.0 Hz coupling was

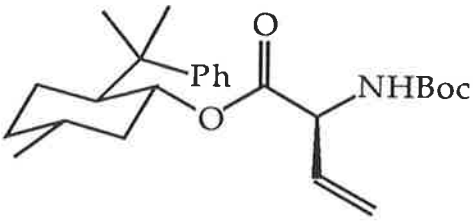
not evident in the α-proton signal due to the broadness of this peak. These couplings are depicted diagramatically in **Figure 19**.

The broad-band decoupled ^{13}C-N.M.R. spectrum of (**90a**) was also consistent with structure (**90**). Besides signals typical of the parent carbon skeleton, resonances at δ 55.52, 116.49 and 132.85 were present. The first of these resonances, confirmed as a tertiary carbon signal by D.E.P.T. spectroscopy, was assigned to the α-carbon. The second signal, due to a secondary carbon nucleus, was due to the terminal vinylic methylene carbon. The third signal was due to the C-3 vinylic methine carbon. Confirmation of the structure (**90**) was made by high resolution mass spectrometry. Under chemical ionization conditions, this compound gave a protonated molecular ion of m/z 416.285, compared to the calculated value of 416.280.

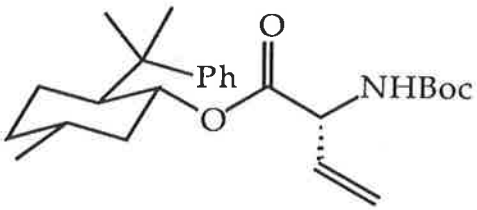
The second-eluting, minor component (**90b**) possessed a ^{1}H-N.M.R. spectrum similar in appearance to that of the major component, but with peaks of different chemical shifts, suggesting that the two compounds were diastereomeric. The α-proton resonated at δ 4.54 as a very broad multiplet. Two slightly broadened doublets centered at δ 5.20 and δ 5.29 (J=10.3 Hz, J=17.4 Hz respectively) were attributed to the terminal vinylic protons. The magnitudes of these couplings indicated that the doublet at δ 5.20 was due to the C-4 vinylic proton *cis* to the C-3 vinylic proton, whilst the doublet at δ 5.29 was due to the C-4 vinylic proton *trans* to the C-3 vinylic proton.

The C-3 proton signal appeared as a doublet of doublets of doublets centred at δ 5.71, with splittings of 5.7 Hz, 10.3 Hz and 17.4 Hz. The two larger couplings are reciprocal to those exhibited by the two terminal vinylic

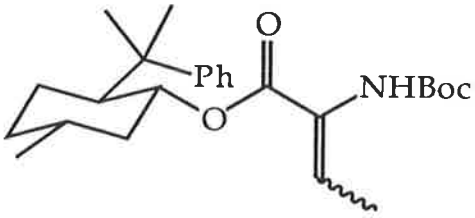
protons, whilst the 5.7 Hz coupling must arise from coupling to the α-proton. This coupling was not evident in the α-proton signal, however, due to the broadness of this peak. These couplings are depicted diagramatically in **Figure 19**. Confirmation of the structure (**90**) was made by high resolution mass spectrometry. Under chemical ionization conditions, this compound gave a protonated molecular ion of m/z 416.281, compared to the calculated value of 416.280.



(**90a**)



(**90b**)



(**95**)

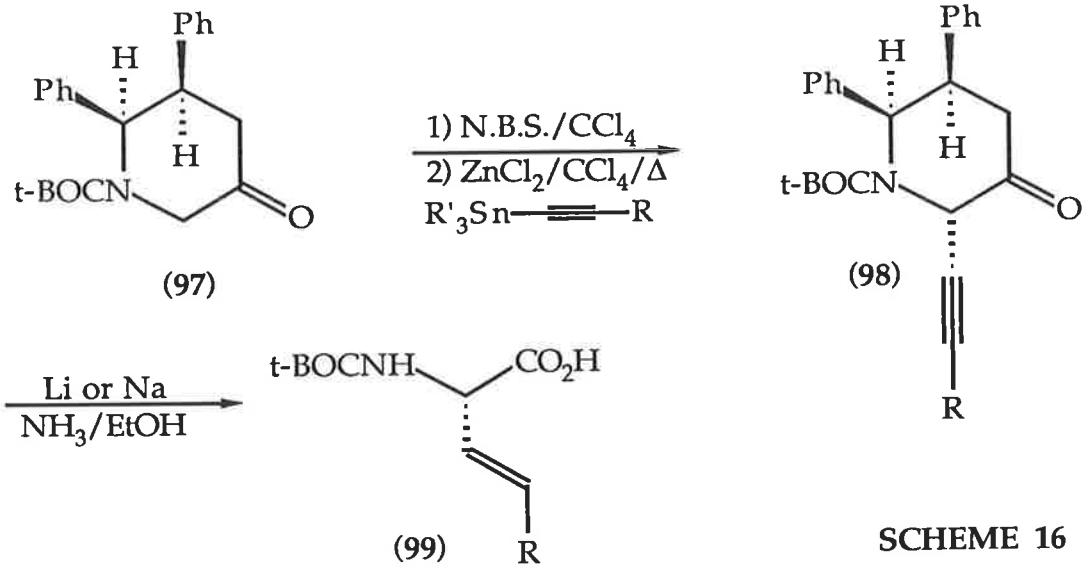
FIGURE 20

Thus, it appeared that the two compounds obtained from vinylmagnesium bromide addition to the α-bromoglycinate (**48**) were the diastereomeric vinylglycine derivatives (**90a**) and (**90b**) (**Figure 20**). The 2-(*S*) stereochemistry was tentatively assigned to the first eluting, major diastereomer due to the precedent set by the chromatographic properties of the other α-substituted 8-phenylmenthyl *N*-*t*-Boc-glycinates in this series. Further evidence that the first-eluting diastereomer possessed the 2-(*S*) stereochemistry was that its α-proton resonated at δ 4.07, 0.47 p.p.m. lower

than the chemical shift of the α-proton of the minor, second-eluting diastereomer. The connection between α-proton chemical shift and C-2 stereochemistry was discussed earlier. The possibility that the α-β-dehydro isomer (**95**) (**Figure 20**) was one of the products was dismissed since this compound has no α-proton, only one vinylic proton and an extra methyl group. These structural features are inconsistent with the spectral data of both of the isolated compounds.

Hydrogenation of the unfractionated mixture of diastereomers (**90a**) and (**90b**) under standard conditions was followed by H.P.L.C. analysis of the reaction product (**96**). Two peaks in the same ratio as the two unsaturated compounds (*ca.* 3:1), but of differing retention times, were detected. Isolation of small amounts of these two components by H.P.L.C. enabled their analysis by ^{1}H-N.M.R. H.P.L.C. and ^{1}H-N.M.R. correlation of the hydrogenated compounds with the authentic 2-(*S*) and 2-(*R*) 8-phenylmenthyl *N*-*t*-Boc-2-aminobutanoates (**78a**) and (**78b**) established that the first-eluting, major saturated compound (**96a**) was identical to the 2-(*S*) α-aminobutanoate (**78a**), and that the minor saturated compound was identical to the 2-(*R*) diastereomer (**78b**). This confirmed that the vinylmagnesium bromide addition reaction produced an excess of the 2-(*S*) diastereomer (**90a**).

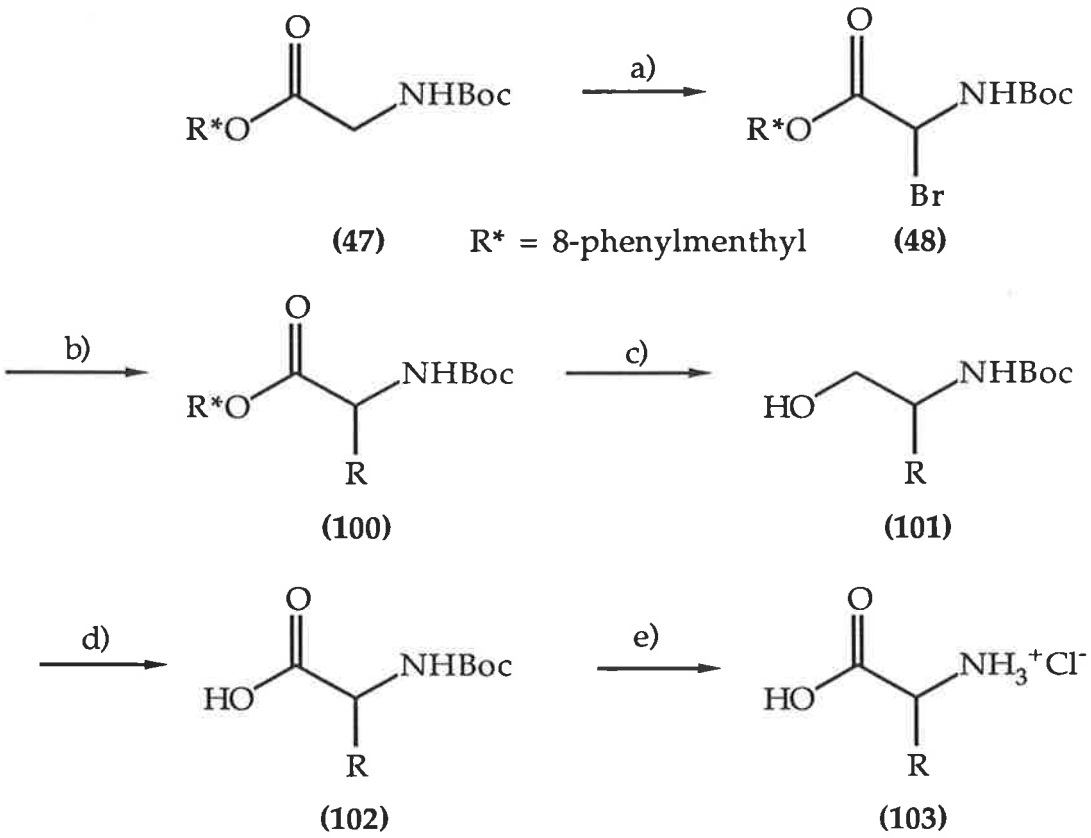
After the completion of this work, the asymmetric synthesis of some vinylglycine derivatives was reported by Williams and Zhai[31] (**Scheme 16**). The zinc chloride catalyzed alkylation of the 2-bromo derivative of (**97**) with trialkyltin acetylides provided access to a large range of β-γ-unsaturated α-amino acids. Dissolving metal reduction of the α-alkynylglycine derivatives (**98**) (formed with >99% d.e.) led to the



SCHEME 16

(*E*)-vinylglycine derivatives (**99**) in good yields. However, reduction and/or derivatization for optical purity determination are thought to be responsible for the enantiomeric purity of these compounds being considerably less than that of their acetylene precursors.

1.4 HYDROLYSIS OF 8-PHENYLMENTHYL (*S*)-*N*-*t*-BOC-ALANINATE (74a)



a) N.B.S., hν, Δ.
b) i) RMgX, Et_2O, 0°C, 5 min. ii) HOAc, -20°C
c) $LiAlH_4$, Et_2O, Δ
d) $RuCl_3/NaIO_4$, CH_3CN/H_2O
e) HCl/Et_2O

SCHEME 17

Before this work reached the publication stage, however, a group of researchers (Ermert, Meyer, Stucki, Schneebeli and Obrecht[74]) working at Hoffmann-La Roche in Switzerland published their account of exactly the same approach to asymmetric α-amino acid synthesis in Tetrahedron Letters. As shown in **Scheme 17**, these workers took 8-phenylmenthyl *N*-*t*-Boc-glycinate (**47**) and brominated it at the α position with N.B.S.

under photolytic conditions. The bromide so obtained was then added to an excess of Grignard reagent in ether to give the amino acid derivatives (**100**).

The authors reported that they were subsequently unable to remove the 8-phenylmenthyl group either by hydrolysis or transesterification without concomitant racemization of the liberated amino acid. Consequently, reductive cleavage of the esters (**100**) with lithium aluminium hydride was carried out, yielding the *N*-*t*-Boc-protected α-amino alcohols (**101**). Oxidation of the alcohols with ruthenium trichloride and sodium periodate afforded the *N*-*t*-Boc-protected amino acids (**102**). Removal of the *t*-Boc group by treatment with ethereal hydrogen chloride gave the amino acid hydrochlorides (**103**). The results for the three published Grignard additions in common with those presented in this thesis are summarized in **Table 4**. The chemical ~~and optical~~ and diastereomeric purities yields of (**100a**), (**100b**) and (**100c**) are very similar to those of (**84**), (**86**) and (**87**) (**Table 2**)

ENTRY	R	No.	YIELD %	D.E. %
1	Me	(100a)	71	92
2	*i*-Pr	(100b)	54	89
3	Ph	(100c)	78	82

TABLE 4

The authors were able to show that the reduction and oxidation procedures did not cause any racemization through epimerization at the α-centre. This means that the enantiomeric excesses of the amino acid hydrochlorides (**103**) (determined by chiral G.C. analysis of the *n*-propyl

ester / *N*-pentafluoropropionamide derivatives) reflect the stereoselectivity of the respective Grignard addition steps.

The bromination and Grignard addition steps just described appear to be, at first glance, chemically identical to the work presented in this thesis. However, close inspection of the published work reveals some important differences. Firstly, the published bromination step involved irradiation of a carbon tetrachloride solution of glycinate (**47**) in the presence of N.B.S. at room temperature. This procedure gave, to quote the authors, "a mixture of two bromides". Presumably this means that the two bromides epimeric at the α-centre were formed. The ratio of the two diastereomers was not reported, nor was the means of analysis (though this probably was ^{1}H-N.M.R.). This contrasts with the bromination step reported here, which selectively gave one of the two diastereomeric bromides (albeit in refluxing carbon tetrachloride).

Secondly, the published Grignard addition step involved addition of the bromide to an excess of Grignard reagent in ether at 0°C and quenching of the reaction mixture five minutes later, at −20°C, with acetic acid. As described earlier, the equivalent step reported here involved addition of the Grignard reagent to an ethereal solution of the bromide cooled to −78°C, followed by quenching two hours later, at room temperature, with saturated ammonium chloride. This procedure resulted in generally higher asymmetric induction, most probably due to the lower reaction temperature. For the three Grignard additions in common with those presented here, however, (MeMgI, *i*PrMgI and PhMgBr) the chemical yields are very similar.

At this stage, it was necessary to decide whether this research was worth pursuing further in light of being beaten to the publication stage. The following factors persuaded us that the project still merited study:

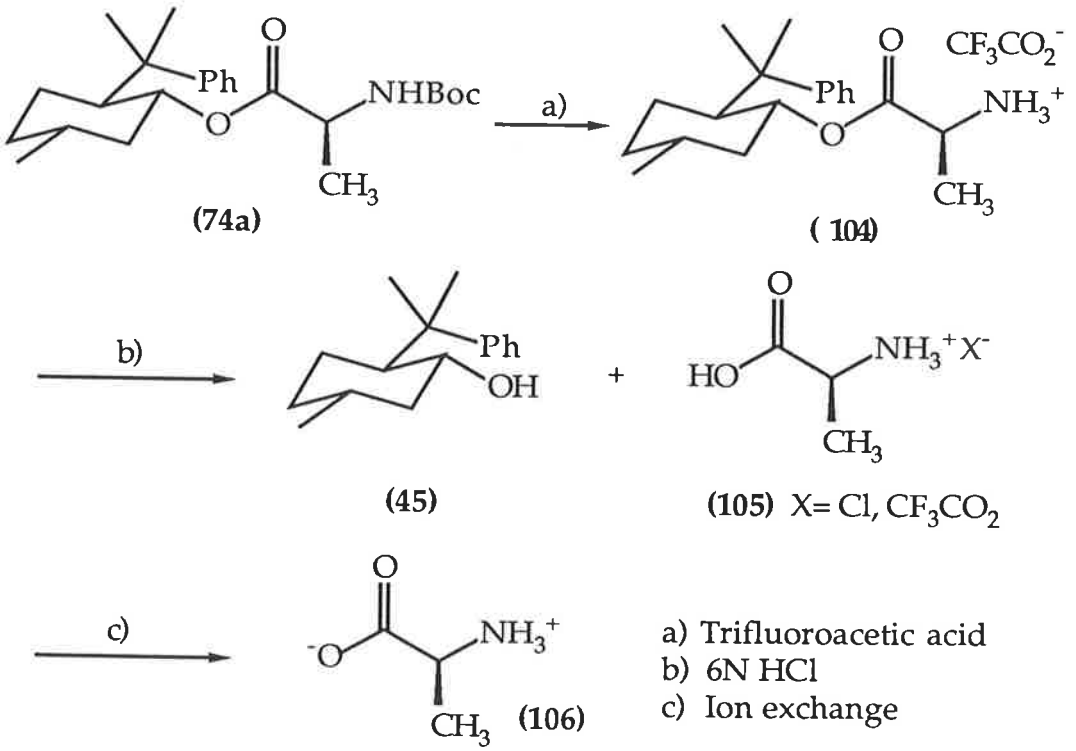
i) In the Swiss authors' hands, (i.e., performing the bromination at room temperature), the α-bromoester (**48**) was acquired as a mixture of two diastereomers. In our hands, (i.e., performing the bromination at 80°C), only one diastereomer was produced. Although the diastereomeric purity of the bromide has no bearing on the diastereoselectivity of Grignard addition (as the chiral centre is destroyed by the elimination of hydrogen bromide), this is an important result when consideration is given to the dearth of examples of high asymmetric induction at radical sites in acyclic systems.

ii) The authors were unable to hydrolyze the amino esters to the corresponding amino acids without racemization. The reduction/oxidation procedure used to circumvent this problem severely limits the range of groups with which the α-bromoglycinate (**48**) can be functionalized. It was felt that if non-epimerizing hydrolysis of the 8-phenylmenthyl esters could be achieved, this work would warrant a full paper, despite the similarity to the Swiss communication.

To this end, the task of developing such a hydrolysis procedure was undertaken. It was envisaged that the hydrolysis of esters (**84**)-(**91**) could be achieved by firstly treating them with trifluoroacetic acid to remove the *N*-*t*-Boc group, generating the corresponding trifluoroacetate salts. It was assumed that these salts would be soluble in aqueous acid and that, once in solution, refluxing for an appropriate length of time would produce the amino acid hydrochlorides. The enantiomeric purity of the liberated

amino acids could then be measured to reveal whether or not the hydrolysis conditions caused epimerization.

The model compound chosen to test this hydrolysis procedure was *N*-*t*-Boc-(*S*)-alanine 8-phenylmenthyl ester (**74a**), prepared from enantiomerically pure (*S*)-alanine. The diastereomeric purity of this ester was confirmed by H.P.L.C. analysis. Under the same conditions which separated the two diastereomeric *N*-*t*-Boc-alanine 8-phenylmenthyl esters (**74a**) and (**74b**), no trace of the 2-(*R*) diastereomer (**74b**) was detected. Analysis of the enantiomeric purity of the alanine produced by hydrolysis of (**74a**) would then reveal whether or not any racemization had taken place under the hydrolytic conditions being used.



SCHEME 18

Accordingly, *N*-*t*-Boc-(*S*)-alanine 8-phenylmenthyl ester (**74a**) was treated with trifluoroacetic acid (**Scheme 18**). After evaporating excess trifluoroacetic acid, the residual trifluoroacetate salt (**104**) was found to be insoluble in 6N HCl. This was surprising, at first, as it is an ammonium salt which one would expect to be water soluble. However, in hindsight, the 8-phenylmenthyl moiety must confer sufficient hydrophobicity to the salt to override the hyrophilic effect of the charged sites, giving rise to the observed insolubility in aqueous acid. In fact, the trifluoroacetate salt (**104**) was found to be soluble in a 19 : 1 hexane/chloroform mixture.

Thus, it was apparent that the hydrolytic solvent needed to be more lipophilic. It was reasoned that a trifluoroacetic acid/6N HCl mixture would dissolve the trifluoroacetate salt due to the lipophilic (relative to 6N HCl) influence of the trifluoroacetic acid. This turned out to be the case. The revised procedure involved treatment of *N*-*t*-Boc-(*S*)-alanine 8-phenylmenthyl ester (**74a**) (*ca.* 100mg) with trifluoroacetic acid (1 ml) for fifteen minutes, followed by the addition of 6N HCl (2 ml) to this solution. Under these conditions, the trifluoroacetate salt was soluble. The homogeneous solution could then be refluxed in an attempt to hydrolyze the ester group of the salt (**104**). It transpired that this procedure successfully effected hydrolysis of (**104**) to give the mixed hydrochloride/hydrotrifluoroacetate (**105**) (**Scheme 18**).

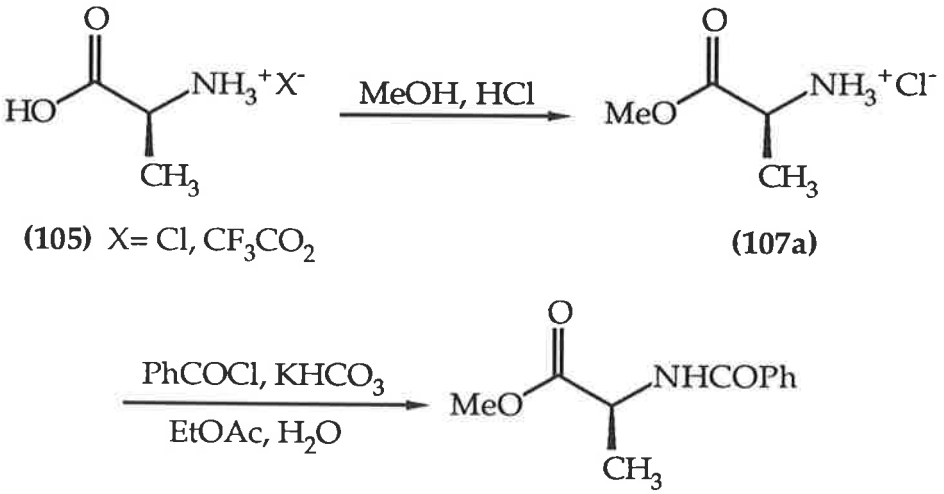
The enantiomeric purity of the hyrolysate was initially determined by polarimetry. This necessitated conversion of (**105**) to the free zwitterionic amino acid (**106**). This was achieved quantitatively by ion exchange chromatography using Amberlite 1R-120 (H), a polysulphonic acid cation exchanger. The free (*S*)-alanine produced had $[\alpha]_D^{20} = +16.1 \pm 0.9^\circ$ (C=3, 1N HCl), compared to the reported value[75] ($[\alpha]_D^{20} = +14.7^\circ$, C=5.8, 1N HCl).

This discrepancy may have been be due to the differing amino acid concentrations employed in the two measurements (5.8g/100ml in the reported case, 3g/100ml in this case). The higher literature concentration could not be duplicated as a limited amount of the alanine derived from hydrolysis of the parent ester (**74a**) was available.

Hence, it was decided to prepare a solution of authentic (*S*)-alanine at a concentration of 3g/100ml in order to determine what effect, if any, the amino acid concentration had on the magnitude of optical rotation. The rotation observed for this solution was $[\alpha]_D^{20} = +16.4^\circ \pm 0.9^\circ$ (C=3, 1N HCl), in close agreement with that for the hydrolysis-derived alanine. This indicated that, within experimental error, the (*S*)-alanine sample obtained through hydrolysis of (**74a**) was enantiomerically pure and, in turn, that the hydrolysis proceeded with no racemization of the alanine moiety. However, this technique obviously could not reveal whether only a few percent of (*R*)-alanine had been produced. Due to the capricious nature of optical rotation measurements and their subsequent inability to reliably determine enantimeric purity to great accuracy, it was decided to employ chiral H.P.L.C. analysis of the hydrolysis derived (*S*)-alanine.

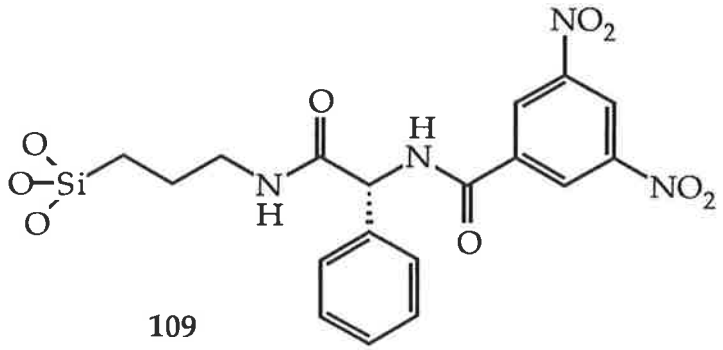
The hydrolysate was derivatized to *N*-benzoyl-(*S*)-alanine methyl ester (**108a**) (**Scheme 19**). Firstly, treatment with methanolic hydrogen chloride gave the methyl (*S*)-alaninate hydrochloride (**107a**). The hydrochloride was converted to its *N*-benzoyl derivative (**108a**) by treatment with benzoyl chloride under Schotten-Baumann conditions. Earlier, it had been found that the corresponding racemic alanine derivative (**108**) (made under the same conditions as those described above) was resolvable into two enantiomers using a chiral "Regis Covalent Pirkle Column" with 9 : 1 light petroleum/2-propanol as the mobile phase (U.V. detector set at 254

nm). The column packing consists of silica modified with the *N*-(3,5-dinitrobenzoyl)-(*R*)-phenylglycine derivative (**109**) shown in **Figure 21**.



(105) X= Cl, CF_3CO_2 **(107a)** **(108a)**

SCHEME 19



109

FIGURE 21

The two enantiomeric solutes participate in diastereomeric interactions of different magnitudes with the ~~homochiral~~ enantiomerically pure packing and hence are eluted at different rates. It is interesting to note that attempts to resolve the *N*-(3,5-dinitrobenzoyl)-(*R,S*)-alanine methyl ester (in an attempt to increase the sensitivity of the analysis by virtue of the more strongly

absorbing 3,5-dinitrobenzoyl chromophore) on the same chiral column had met with failure. Presumably, the interaction between the aromatic ring of the solute molecules and the aromatic ring of the stationary phase are critical to the efficient separation of enantiomers by this column. Changing the electronic nature of the aromatic ring of the amino acid derivative, as evidenced here, can dramatically effect the enantiomer resolution.

A series of hydrolyses was performed with variation of reaction time in order to optimize chemical and optical yields. The results are summarized in **Table 5**. In all cases, even when the hydrolysis time was extended to fifteen hours (the optimum hydrolysis time; extension beyond fifteen hours did not improve the yield of (**105a**), no racemization of the liberated alanine occurred (i.e. only one enantiomer was detected by chiral H.P.L.C. analysis of the alanine derivative (**108a**)). The configuration of the enantiomer obtained from the hydrolysis was confirmed as (*S*) by co-elution of (**108a**), derived from the hydrolysate (**105**), with an authentic sample derived from (*S*)-alanine.

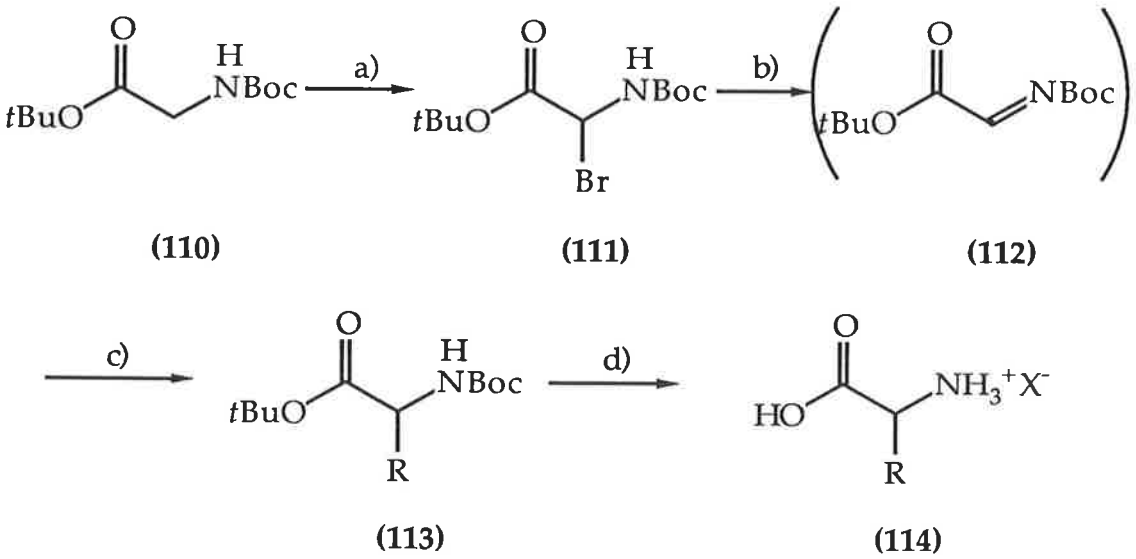
ENTRY	TIME (HR.)	YIELD (105a) (%)	E.E. (108a) (%)[b]
1	1	29	>99
2	2.5	63	>99
3	15	77	>99

a) Yield of crude hydrochloride/hydrotrifluoroacetate salt (**105a**).

b) Determined by chiral H.P.L.C. analysis of the derivative, methyl *N*-benzoyl-alaninate (**108a**).

TABLE 5

1.5 *N*-ACYLIMINOACETATES : OTHER PUBLICATIONS



(110) **(111)** **(112)**

(113) **(114)**

a) N.B.S., CCl_4, hv, 20°C. b) RMgX, T.H.F., -78°C.
c) i) RMgX, T.H.F., -78°C to R.T. ii) H_3O^+.
d) T.F.A., 50°C or 6N HCl, Δ.

SCHEME 20

During the course of this work, we became aware of a publication by Steglich and coworkers[76], in which the authors reported that the alkylation of *N*-*t*-Boc-2-bromoglycine tertiarybutyl ester (**111**) in T.H.F. solution at –78°C with a variety of Grignard reagents proceeded in 31-91% yields (**Scheme 20**). Furthermore, the bromoester (**111**) was produced as a crystalline solid by free radical bromination of the parent glycine derivative (**110**) with N.B.S. under photolytic conditions at room temperature. This approach to racemic α-amino acid synthesis is conceptually identical and synthetically very similar to the approach to asymmetric α-amino acid synthesis adopted by us. Some synthetic differences are:

i) Steglich *et al.* performed the bromination step at room temperature (c.f. 77°C).

ii) T.H.F. was used as the solvent (c.f. ether) in the Grignard addition reaction.

iii) After completion of Grignard reagent addition, the mixture was allowed to warm slowly to room temperature over twelve hours (c.f. two hours at –78°C, followed by rapid equilibration to room temperature).

iv) Quenching of the Grignard reagent addition was achieved with glacial acetic acid (c.f. saturated ammonium chloride solution).

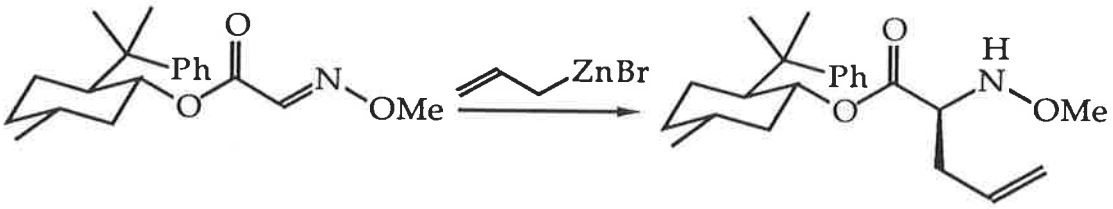
Table 6 compares the yields obtained by Steglich's group and those obtained by us, for those Grignard reagents common to both studies. As is evident, the yields differ significantly, with our approach giving better yields in three of the four cases. Any or all of the synthetic differences between the two methods may well be responsible for the yield differences.

ENTRY	R	YIELD (113) (%)	No.	YIELD (%)
1	Et	51	89	82
2	*i*-Pr	31	86	51
3	Ph	62	87	82
4	Vinyl	61	90	52

TABLE 6

Also during the course of this work, Yamamoto and Ito[77] reported that the alkylation of 8-phenylmenthyl *N*-methoxy-iminoacetate (**115**) with allylzinc gave the adduct (**116**) with good diastereomeric excess

(**Scheme 21**). This prochiral imine induced the (*S*) chirality at the α-centre. This is the same face selectivity displayed by the *N*-*t*-Boc-iminoacetate (**49**)



(**115**) (**116**)

SCHEME 21

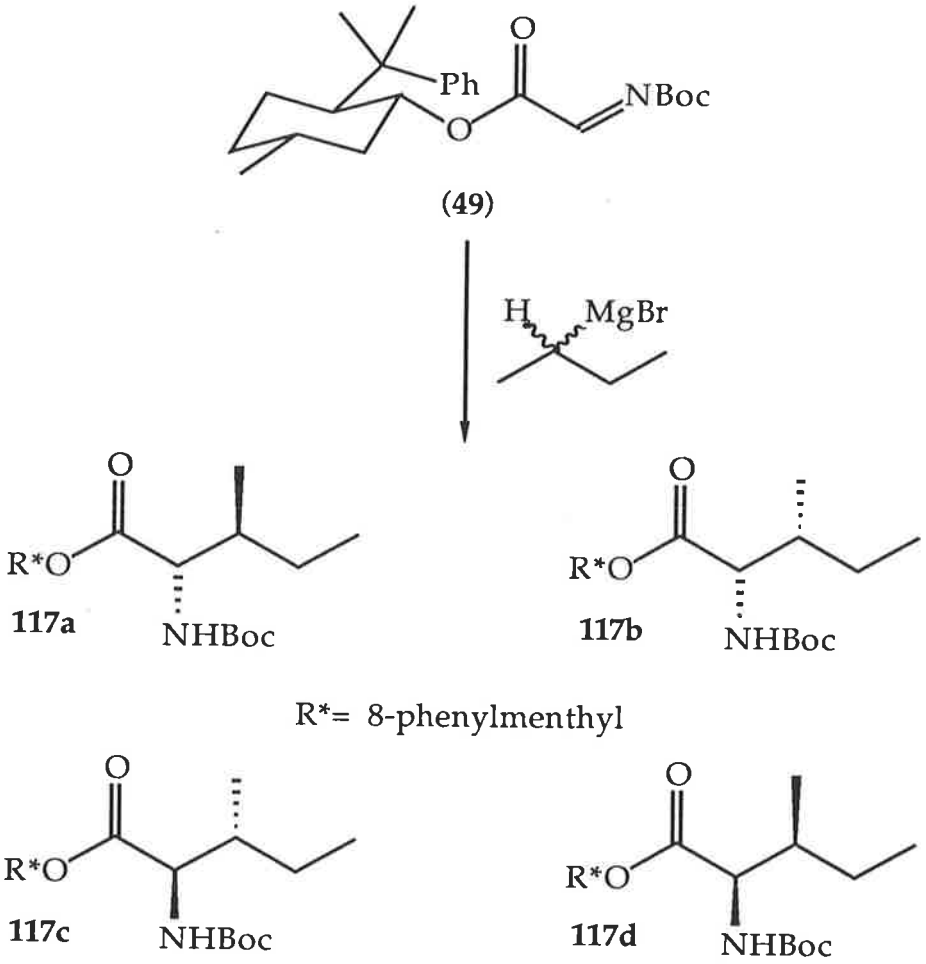
employed in this project. The authors invoked chelation of the ester carbonyl oxygen and imino nitrogen by zinc ion to explain the inferred preference for the *syn* relationship between these two atoms. Interestingly, the 74% diastereomeric excess obtained with allylzinc by these workers was significantly higher than the 57% d.e. obtained when 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate (**48**) was treated with allylmagnesium bromide.

1.6 ADDITION OF A CHIRAL GRIGNARD REAGENT TO BROMIDE (48)

Having demonstrated that 8-phenylmenthyl *N*-*t*-Boc-iminoacetate (**49**) undergoes highly diastereoselective *si* face alkylation by Grignard reagents, it was decided to attempt an extension of this methodology. Addition of the chiral (but racemic) Grignard reagent *sec*-butylmagnesium bromide to the iminoacetate (**49**) could potentially give rise to the four diastereomeric isoleucine derivatives (**117a-d**) (**Scheme 22**). However, since addition takes place selectively at the *si* face of (**49**), the two 2-(*R*) compounds (**117a**) and (**117b**) should be formed in relatively minor proportions. The question of the selectivity at the β-centre then remained to be addressed.

For high asymmetric induction to occur at the β-centre, kinetic resolution of the Grignard reagent must take place. That is, one enantiomer of the Grignard reagent must selectively alkylate the iminoacetate (**49**). For this to occur, racemization of the Grignard reagent through inversion at the metallated centre must be slowed or even stopped. In addition, one of the enantiomeric Grignard species must react substantially faster than the other with the iminoacetate.

Secondary Grignard reagents are reported to be configurationally stable for hours at ambient temperatures in favourable cases[78]. Therefore, if addition of *sec*-butylmagnesium bromide to the iminoacetate (**49**) is performed at low temperature, one would expect that the probability of the Grignard reagent being configurationally stable under these conditions would be high.



SCHEME 22

Accordingly, two equivalents of *sec*-butylmagnesium bromide were added to the bromide (**48**) at −78°C. Reaction conditions identical to those previously established gave the addition product (**118**) in 38% yield. This low yield was similar to that obtained with isopropylmagnesium iodide (51%). These results indicate that secondary Grignard reagents tend to give low yields of Grignard addition products in these reactions.

The product obtained was characterized by ^{1}H-N.M.R. and H.P.L.C. correlation with authentic samples of the isoleucine derivates (**117a-d**). These standards were originally synthesized in order to analyze a reaction

which will be discussed in a later chaper, and their characterizaiton is best described in the context of this later problem. Suffice it to say that the two 2-(*S*) isomers (**117a**) and (**117b**) were coincident by H.P.L.C. analysis, whilst the two 2-(*R*) isomers eluted separately. Furthermore, the four diastereomers were distinguishable by ^{1}H-N.M.R. by virtue of the fact that their α-proton resonances were distinct. This enabled determination of the amount of each diastereomer in the Grignard reaction product. H.P.L.C. analysis of the Grignard addition product (**Figure 22**) indicated that the total 2-(*S*) : 2-(*R*) ratio was high, as expected. Also shown in **Figure 22** is the region of the ^{1}H-N.M.R. spectrum containing the α-proton signals of the (2*S*,3*S*) and (2*S*,3*R*) diastereomers (**117a**) and (**117b**). Clearly, no measurable asymmetric induction had occurred at the β-centre, as evidenced by the 1:1 integration of the two signals.

It was reasoned that the use of only two equivalents of Grignard reagent may have been the cause of the low selectivity at the β-centre, even if *sec*-butylmagnesium bromide at this temperature was configurationally stable. Elimination of hydrogen bromide from the bromide (**48**) generates the imine (**49**). Assuming that elimination is not effected selectively by one of the enantiomeric Grignard species, this leaves half an equivalent of each enantiomer to add to the imine. Under these conditions, no kinetic resolution could be achieved.

In an effort to discover if this argument was valid, three equivalents of *sec*-butylmagnesium bromide were added instead. The rationale behind this experiment was that elimination of hydrogen bromide by one equivalent of Grignard reagent would leave one equivalent of each enantiomeric Grignard species. This would allow for selective alkylation of the imine by one enantiomer. Addition of excess saturated ammonium

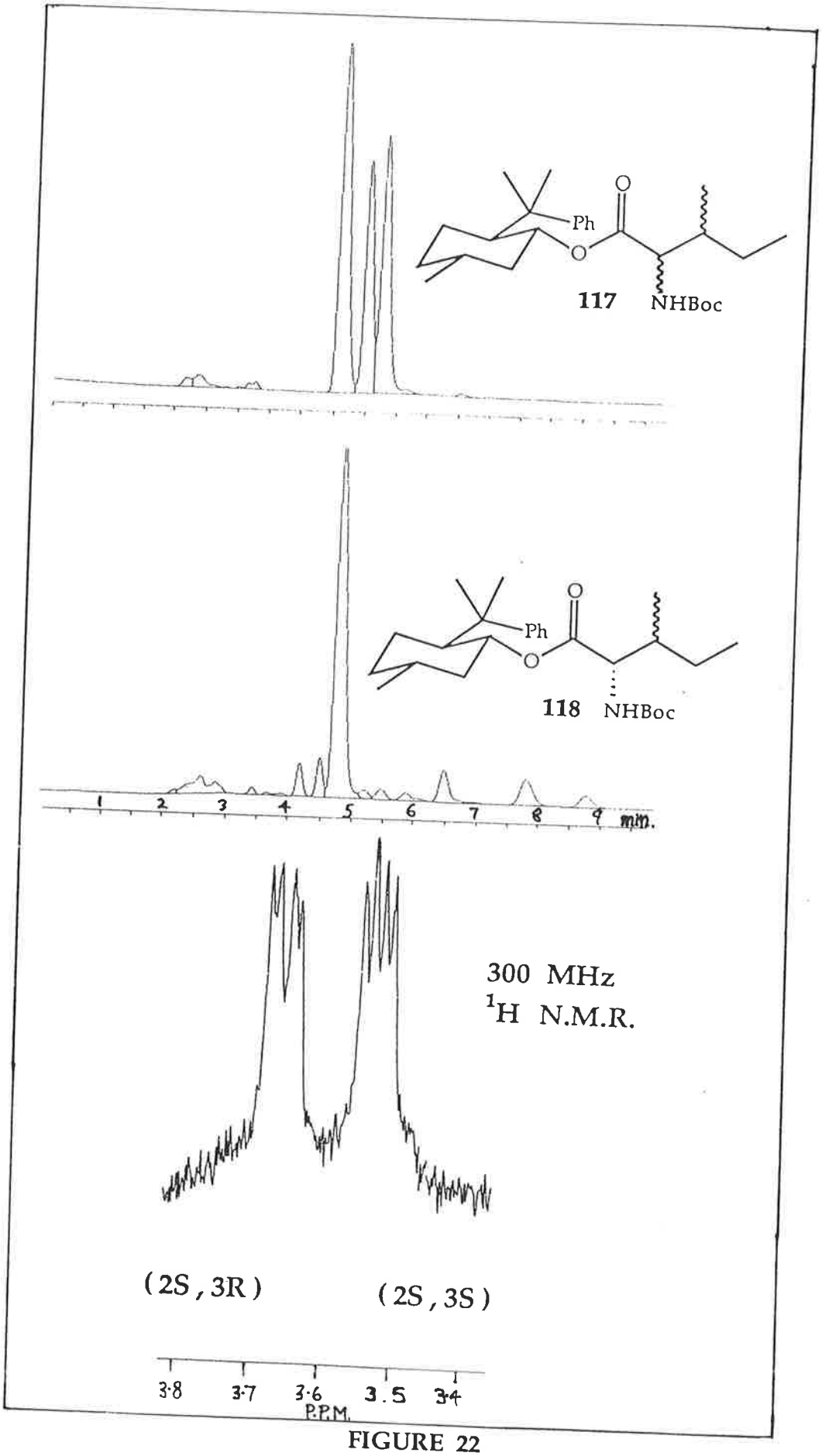

Ph
O
O
117
NHBoc
Ph
O
O
118
NHBoc
1
2
3
4
5
6
7
8
9
min.
300 MHz
^{1}H N.M.R.
(2S, 3R)
(2S, 3S)
3·8
3·7
3·6
3.5
3·4
P.P.M.

FIGURE 22

chloride solution to the reaction mixture at low temperature would then quench the remaining one equivalent of Grignard reagent.

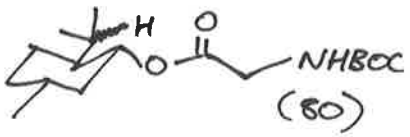
However, analysis of the product obtained under these reaction conditions (in 51% yield) revealed that the (2*S*:3*S*):(2*S*,3*R*) ratio obtained was again 1:1, although the total 2-(*S*):2-(*R*) ratio remained high. As a result, these investigations were not pursued further.

Even if the Grignard reagent was configurationally stable at –78 °C, the small size difference between the methyl and ethyl groups of the Grignard reagent could have resulted in low discrimination between the two enantiomers by the chiral iminoacetate (**49**). This, in turn, would be manifested in there being no appreciable rate difference between the reaction of the imine with either enantiomer of the Grignard reagent.

1.7 INVESTIGATION INTO THE DIASTEREOMERIC PURITY OF BROMIDE (48)

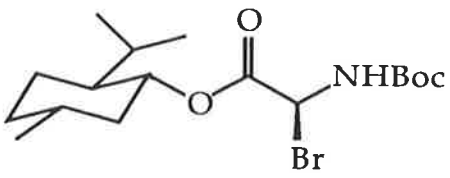
The report by the Swiss group[74] that, in their hands, bromination of 8-phenylmenthyl *N*-*t*-Boc-glycinate (**47**) with *N*-bromosuccinimide gave a mixture of diastereomeric bromides contrasted with our observation that the reaction apparently gave a single diastereomer. This prompted re-examination of this reaction on our part.

A great deal of mainly spectroscopic evidence was acquired which strongly inferred that the bromination proceeded with high diastereoselectivity. As previously discussed, esterification of racemic *N*-*t*-Boc amino acids with (–)-8-phenylmenthol produced diastereomeric esters which were quite clearly differentiable by high field ^{1}H and ^{13}C-N.M.R. Therefore, if a mixture of diastereomers was produced in the bromination reaction, there was little doubt that both diastereomers would be evident by N.M.R. spectroscopic analysis.

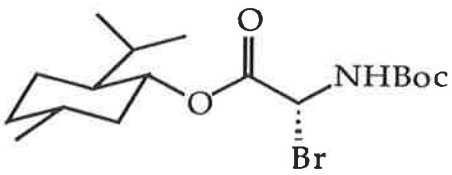


(80)

N-*t*-Boc-glycine (–)-menthyl ester (**80**) was brominated under the same conditions as those employed for the (–)-8-phenylmenthyl analogue (**47**) (treatment with one equivalent of *N*-bromosuccinimide in carbon tetrachloride at reflux under photolysis for ten minutes), as discussed earlier. The ^{1}H-N.M.R. spectrum of the bromides (**48**) and (**81**) were run in carbon tetrachloride solution, simply because this was the most expedient solvent for these compounds. Since the bromination reactions were performed in carbon tetrachloride, and it was desirable that manipulation of these labile compounds be kept to a minimum, removal of succinimide by filtration was followed by rapid N.M.R. analysis of the filtrate.



(81a)



(81b)

FIGURE 23

^{1}H-N.M.R. analysis of **(81)** indicated that an almost 1:1 mixutre of the diastereomeric α-bromides **(81a)** and **(81b)** resulted (**Figure 23**). Two overlapping doublet signals centred at δ 6.18 and δ 6.17, each exhibiting a coupling constant of 10.6 Hz, were attributed to the α-protons of the two diastereomers. Each of these protons are, of course, coupled to an amide proton. Although only one amide proton resonance was present in the spectrum (at δ 5.74, J=10.6 Hz), the broadness of this signal was indicative of two overlapping doublets. Two partially overlapping doublets of triplets centred at δ 4.73 and δ 4.67 were also evident, and these signals were attributed to the C-1' alkoxy ester proton of each diastereomer. Both of these multiplets displayed coupling constants of 4.4 Hz and 11.0 Hz.

Four signals due to the geminal C-9' and C-10' methyl groups were detected. In the 8-phenylmenthyl case, the equivalent methyl protons had no proton at C-8' with which to couple, and consequently gave singlet resonances. In the menthyl case outlined here, the presence of the C-8' proton meant that the C-9' and C-10' methyl signals were doublets. The downfield pair of doublets appeared at δ 0.97 and δ0.95 with a 9.3 Hz splitting, whilst the upfield doublets were centred at δ 0.92 and δ 0.91 and exhibited a 7.2 Hz coupling constant. Two overlapping doublets due to the C-7' methyl groups of each diastereomer, each with J=6.9 Hz, were also present in the spectrum. Although only one tertiarybutyl methyl

resonance was evident (situated at δ 1.48), the broadness of this peak was consistent with the presence of two diastereomers.

Quite clearly, the menthyl glycinate (**80**) was brominated at the α-position stereorandomly. Furthermore, the two diastereomers were differentiable by ^{1}H-N.M.R. One would expect (–)-8-phenylmenthol to be at least as powerful a chiral auxiliary as (–)-menthol with respect to distinguishing between diastereomers by N.M.R. Hence, the observations outlined above reinforce the expectation that, should bromination of 8-phenylmenthyl *N*-*t*-Boc-glycinate (**47**) give a mixture of diastereomeric α-bromides, both diastereomers would be clearly discernable by ^{1}H-N.M.R.

The ^{1}H-N.M.R. spectrum of 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate was also run at 300 MHz in CCl_4. Only one tertiarybutyl resonance (situated at δ 1.50), one pair of geminal methyl group resonances (at δ 1.29 and δ 1.20) and one ring methyl doublet (centred at δ 0.94 p.p.m., J=6.5 Hz) were clearly discernable. In addition, only one amide doublet (δ 5.45, J=10.7 Hz), one α-proton doublet (δ 4.87, J=10.7 Hz) and one doublet of triplets due to the alkoxy ester proton at C-1' (δ 4.82 Hz, 10.8 Hz) were present. Thus, as far as could be discerned without a sample of the bromide epimeric with the major diastereomer available, the bromination of (**47**) proceeded with very high asymmetric induction. The exact degree of diastereoselectivity could not be established, since ^{1}H-N.M.R. showed no sign of the ~~major~~ minor diastereomer and chromatographic analysis was precluded by the lability of the α-bromoglycinate.

^{13}C-N.M.R. analysis of the bromide (**48**) in carbon tetrachloride solution confirmed that mainly one diastereomer had been formed. The spectrum obtained was consistent with the expected structure. Some extraneous

peaks were present in the spectrum, but it was not clear whether these peaks were due to α-epimer or an entirely different species. In any case, these extraneous signals were of low intensity and, at worst, represented an impurtity of *ca.* 5%. Two signals which were expected but did not appear were those of the quaternary aromatic carbon and one of the geminal methyl carbons. The absence of the former signal, which was expected to resonate between δ 154.5 and δ 155.5 with extremely low intensity (based on the precedent set by the other compounds in this series), is probably due to the poor relaxation of the quaternary nucleus. The missing methyl signal was probably obscured by another methyl signal. The most likely peak responsible for this was the tertiarybutyl methyl signal at δ 28.02. The α-carbon resonated at δ 53.70.

In the aromatic region of the spectrum, five tertiary phenyl carbon resonances were observed. Three of these resonances (at δ 124.74, 125.14 and 125.44, in a *ca.* 5:1:1 ratio of intensities) appeared in the "*ortho, para*" carbon region. The remaining two peaks (at δ 127.59 and 127.78, in a *ca.* 4:1 ratio) were situated in the "*meta*" carbon region. These data are contrary to the expectation that, due to the symmetry of the phenyl substituent, only three tertiary phenyl carbon resonances should arise. This can only be so, however, if free rotation of the phenyl ring is possible. It is tempting to suggest that the presence of five resonances is due to restricted rotation of the aromatic ring. If this did occur, one would expect that the resultant difference between the chemical (and therefore magnetic) environments of the two *ortho* carbon nuclei would manifest itself in the presence of two different *ortho* carbon signals in the ^{13}C-N.M.R. spectrum. The same argument, of course, would apply in the case of the two *meta* carbon nuclei.

The possibility does exist that these additional aromatic signals are due to the presence of another compound, either the epimeric bromide or an entirely different species. This is considered unlikely, however, since the rest of the spectrum is devoid of any contaminant resonances of similar intensity. Why the inferred restricted rotation of the phenyl group should occur in this compound and not in any other of the related compounds in this series is a matter for speculation. A possible explanation is that the carbon-bromine bond of the bromide (48) is weakened by the influence of the nitrogen lone pair electrons. It may be that the subsequent development of partial double bond character in the α-carbon-nitrogen bond, along with concommitant development of a partial positive charge on nitrogen, leads to interaction with the π electrons of the aromatic ring. This type of interaction would account for the restricted rotation of the aromatic ring.

Clearly, a discrepancy existed between the report by Ermert *et al.*[74] that the bromination of (47) gave a mixture of diastereomers and our finding that only one diastereomer was obtained. The fact that the Swiss group had performed the bromination at room temperature, as opposed to the refluxing carbon tetrachloride conditions employed by us, led to speculation as to whether or not this temperature difference was responsible for the differing stereochemical outcomes.

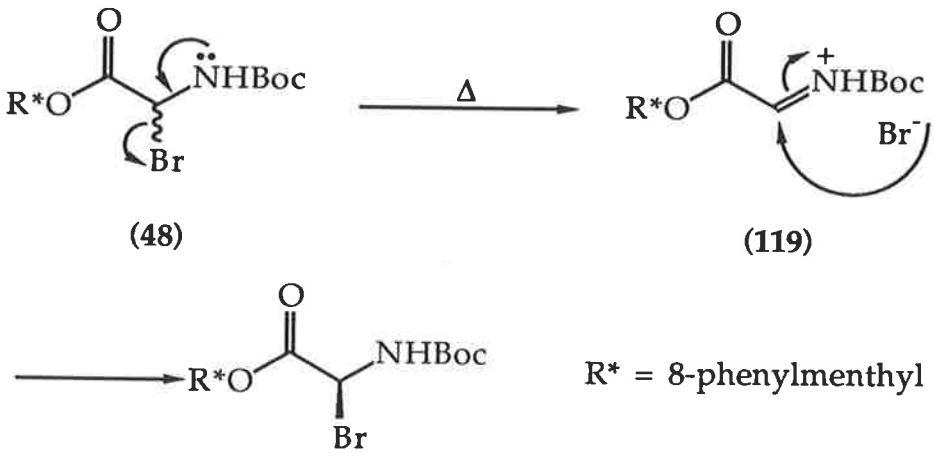
Since α-bromoglycinates are known to undergo thermal equilibration[79], it was considered that equilibration of a first-formed mixture of diastereomers may well have been responsible for the asymmetric induction observed by us. In an attempt to establish that this was so, the chiral glycinate (47) was brominated with N.B.S. under photolytic conditions for thirty minutes at room temperature. After cooling on ice

and removal of succinimide by filtration, the product was analyzed by ^{1}H-N.M.R. at 300 MHz in carbon tetrachloride solution. The spectrum obtained indicated that starting material had been completely consumed. Furthermore, the presence of a mixture of diastereomeric α-bromides was inferred. In addition to the signals observed in the spectrum of the product of the high temperature reaction, an extra set of signals consistent with the structure of the epimeric bromide was observed. The intensity of these signals indicated that this compound constituted *ca.* one quarter to one third of the mixture.

The tertiarybutyl methyl signal of the minor diastereomer appeared at δ 1.46, whilst the two singlets due to the geminal methyl groups were situated at δ 1.24 and δ 1.15. A doublet due to the ring methyl group was centred at δ 0.90 (J=6.3 Hz). The C-1' alkoxy ester proton, amide proton and α-proton of this compound were obscured by the corresponding signals of the major diastereomer. Thus it appears that, under non-equilibrating conditions (i.e., room temperature) a kinetic mixture of bromides is obtained. From the ^{1}H-N.M.R. data, it appears that the ratio of diastereomers produced by homolytic bromine atom transfer to the α-centred radical is *ca.* 3 : 1. The fact that one diastereomer is obtained at elevated temperatures suggests that equilibration of the mixture occurs, most probably *via* the mechanism shown in **Scheme 23**.

That this ionic mechanism should be more selective than the radical mechanism, even at elevated temperatures, is not surprising as the α-carbon to nitrogen bond of the intermediate iminium ion (**119**) would be expected to possess greater double bond character than that of the corresponding α-centred radical (**120**) (**Figure 23a**). Hence, (**119**) is less conformationally mobile than (**120**). This would result in the *si*

diastereoface selectivity of bromide ion addition to the iminium ion (**119**) being greater the *si* diastereoface selectivity of bromine atom addition to the radical (**120**)

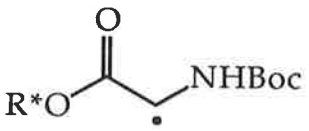


(**48**) (**119**)

(**48a**)

R* = 8-phenylmenthyl

SCHEME 23



R* = 8-phenylmenthyl

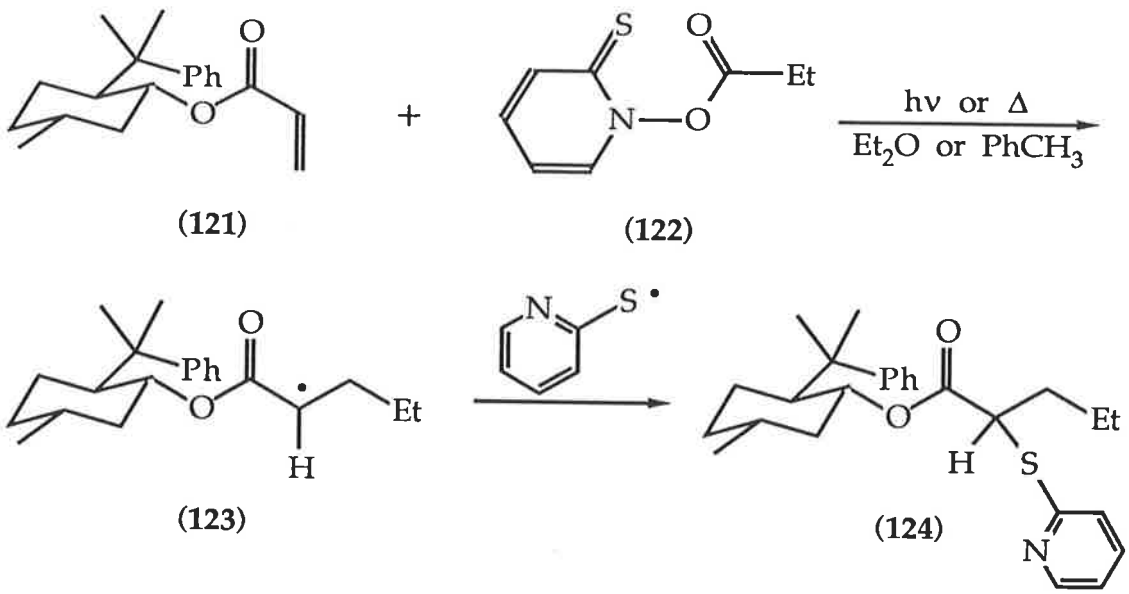
(**120**)

FIGURE 23a

Chapter 2 - Introduction

The observation that the bromination of 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate with *N*-bromosuccinimide under homolytic conditions proceeded with asymmetric induction was a very exciting one. This synthon has the potential to yield α-amino acid derivatives not accesible by the Grignard chemistry just described. Hence, reactions suitable for the elaboration of the bromide (**48**) *via* radical pathways will be investigated. As well as potentially providing novel α-amino acids, these reactions may eliminate the ambiguity created by some of the observations made regarding the bromination reaction. As discussed earlier, it appeared that the high diastereoslectivity of this reaction was the result of thermodynamic equilibration of a first-formed *ca*. 3 : 1 mixture of diastereomeric bromides (**48a**) and (**48b**). Formation, through a radical pathway, of a derivative which is incapable of such equilibration should give a ~~truer~~ precise indication of the diastereoselectivity of the reactions of the α-centred radical (**120**).

In addition to providing access to a range of novel α-amino acid derivatives, this chemistry is worth pursuing since it embraces the little-explored field of asymmetric, acyclic radical reactions. The control of relative stereochemistry in radical reactions such as 1,5 cyclizations[80,81] is now commonplace and is well understood. Control of absolute stereochemistry in the intermolecular reactions of radicals in cyclic systems with radicalophiles has also been abundantly demonstrated[82]. There are relatively few reports, however, of radicalophiles exhibiting diastereofacial selectivity at radical centres in acyclic systems[83,84].

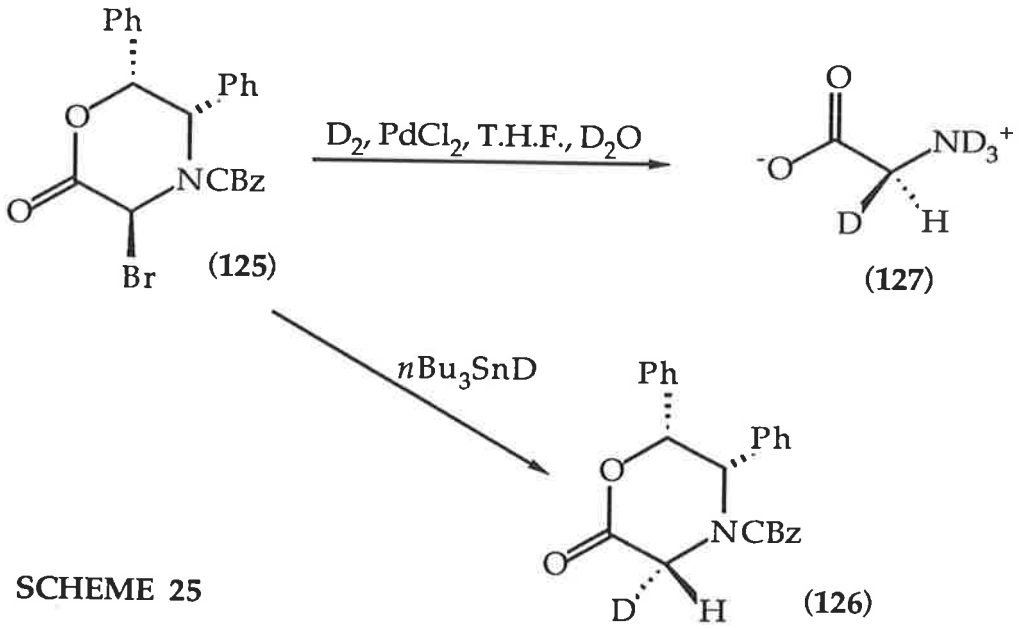


SCHEME 24

Significantly, one of these reports concerned 8-phenylmenthyl acrylate **(121)**[84] **(Scheme 24)**. Addition of ethyl radical (generated by thermolysis of the *O*- acyl thiohydroxamate **(122)** in toluene) to the α position of the acrylate double bond generated the intermediate radical **(123)**. Combination of this radical with *S*-pyridyl radical gave the adduct **(124)** in 30% d.e. With photochemical initiation at 10°C in ether, the d.e. was improved to 56%. The configuration of the new chiral centre was, however, not stated by the authors. Nevertheless, this work demonstrated that 8-phenylmenthol was capable of controlling absolute stereochemistry in acyclic radical reactions.

The dearth of reports of asymmetric induction at acyclic radical centres is the result of two factors. Firstly, this area is still somewhat in its infancy. Secondly, in order to achieve useful levels of asymmetric induction, special factors are necessary to restrict the conformational mobility of the open chain. Whilst the factors controlling absolute stereochemistry in acyclic polar reactions are well understood, only recently has a similar level of understanding of acyclic radical reactions begun to be approached.

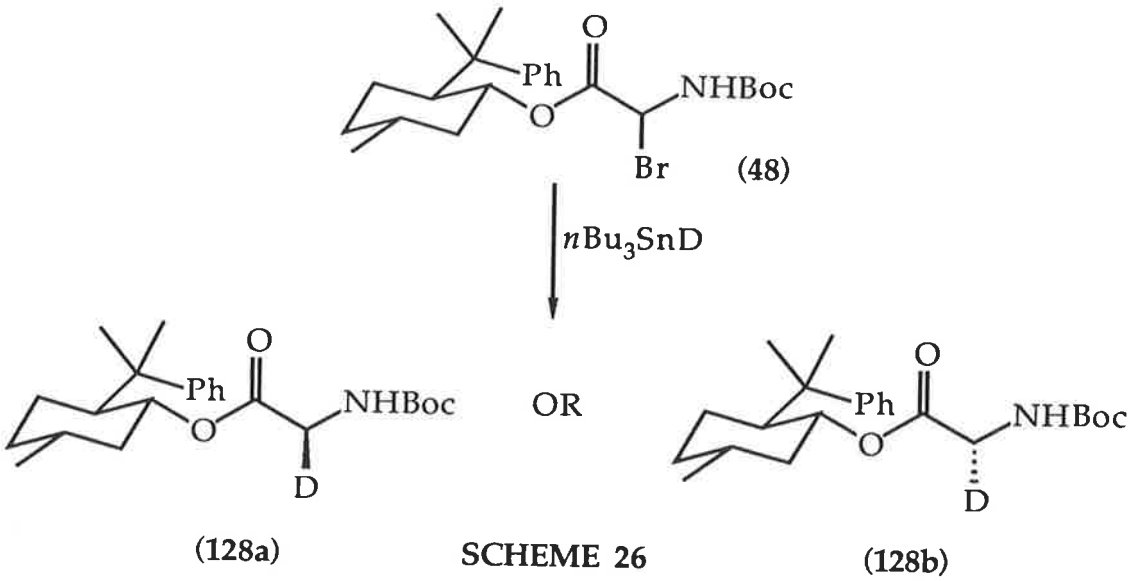
Tri-*n*-butyltin deuteride has been shown to be capable of reducing α-bromoglycine moieties by means of a radical chain mechanism[85]. In fact, Williams and coworkers[11] have reduced the bromide (**125**) with nBu$_3$SnD to give, after deprotection of (**126**), (*R*) chiral glycine in 60% e.e (**Scheme 25**).



SCHEME 25

New routes to the synthesis of chiral glycine are still continually sought[86]. This is because many existing routes are long and do not give a product of high optical purity. Homochiral glycine is required[86] as a probe for the elucidation of biosynthetic pathways, enzymic mechanisms and the conformations of peptides in solution. It is also useful as an intermediate in the synthesis of other important labelled compounds such as ~~homo~~chiral acetic[87] and ~~homo~~chiral glycolic[88] acids.

Despite this, a short, efficient synthesis of homochiral glycine remains elusive. Perhaps the best so far is that of Williams[11], which involves treatment of the α-bromoglycine derivative (**125**) with D_2 (**Scheme 25**). The e.e. obtained for chiral (*S*) glycine (**127**) was 77-82%.



(128a) **SCHEME 26** (128b)

Reduction of the bromide (**48**) with readily available tri-*n*-butyltin deuteride[89] has the potential to yield the corresponding α-deuterioglycine derivative (**128a**) or (**128b**) in high optical purity (**Scheme 26**). This requires a diastereoselective abstraction of deuterium atom by the α-centred radical (**120**). Both efficient diastereoface blocking by the chiral auxiliary and restricted rotation of the σ bonds labelled **a**, **b** and **c** in **Figure 24** are necessary for this to occur.

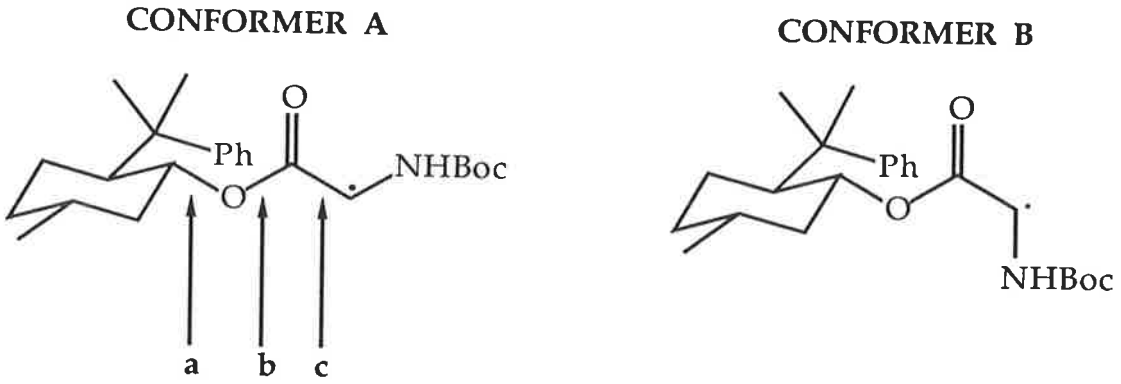


FIGURE 24

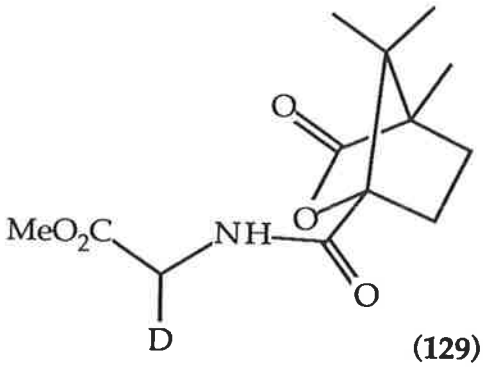
The power of 8-phenylmenthol as a diastereoface blocker has been abundantly demonstrated, as has the preference for a variety of

8-phenylmenthyl esters to have the ester carbonyl group in a *syn* coplanar arrangement with the alkoxy C-H bond of the 8-phenylmenthol moiety[46-55] (**Figure 24**). This conformation is inferred by the configuration of the chiral sub-units formed in the asymmetric reactions of 8-phenylmenthyl esters. The high diastereoselectivity of these reactions indicate that rotation about bonds **a** and **b** is significantly restricted.

It is expected that rotation about bond **c** will also be restricted as this bond has partial double bond character due to delocalization of the unpaired electron into the ester carbonyl group[90,91] (the capto effect). Resonance contributors (**35**) and (**37**) (**Figure 7**, Chapter 1Introduction) clearly show this.

Whether the α-centred radical adopts conformation **A** or **B** (**Figure 24**) should be inconsequential to the level of diastereoselectivity; it is important only that one of these conformers predominates. Putting the efficiency of the chiral auxiliary aside, the magnitude of the rotational barrier in bond **c** will determine the ratio of the two conformers and hence the degree of diastereoselectivity in the deuteration step.

Determination of the ratio in which (**128a**) and (**128b**) are produced should be possible by ^{1}H-N.M.R. spectroscopy. As discussed earlier, the signals due to each diastereotopic α-proton of the parent glycine derivative (**47**) are distinguishable by 300 MHz ^{1}H-N.M.R. Hence, the α-proton signals of the two diastereomeric chiral glycine derivatives (**128a**) and (**128b**) should also be distinguishable at this field strength. Integration of the two signals will then allow for the determination of the percentage of each diastereomer.



(129)

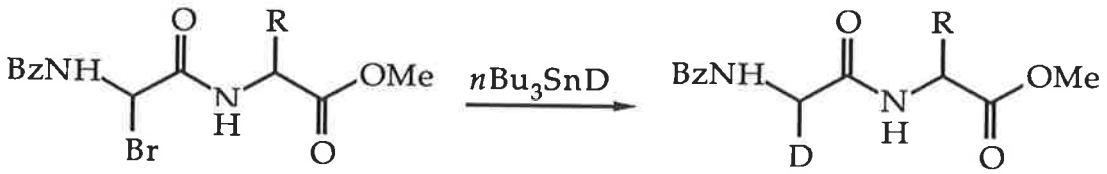
FIGURE 25

Hydrolysis of (**128a**) or (**128b**) would yield free (*S*) or (*R*) ~~homochiral~~ glycine. The absolute configuration of the chiral glycine obtained can be determined by synthesizing (**129**) (**Figure 25**), the procedure for which is outlined by Armarego[92]. The pro-(*S*) α-proton of (**129**) is reported to resonate at higher field than its pro-(*R*) partner. If successful, this approach would provide a very short and hopefully efficient synthesis of enantiomerically pure ~~homo~~chiral glycine.

Chapter 2 Results and Discussion

2.1 (*S*)-2-DEUTERIOGLYCINE

Tri-*n*-butyltin deuteride was synthesized by the method of Kuivila and Beomel[89], who produced tri-*n*-butyltin hydride by lithium aluminium hydride reduction of tri-*n*-butyltin chloride. Use of lithium aluminium deuteride (99 atom%) instead gave tri-*n*-butyltin deuteride in 69% yield after distillation.



(130) **(131)**

R= *i*Pr, *i*Bu, Bn, $CH_2CO_2CH_3$, 37-54%

SCHEME 27

Easton *et al*[85] had reported the reduction of α-brominated dipeptides such as (130) with tri-*n*-butyltin deuteride (**Scheme 27**) at room temperature, without the use of a radical initiator. Presumably, the stability of capto dative radicals of the type involved here is such that carbon-bromine bond homolysis occurs spontaneously even at ambient temperature. This observation, along with the general need for low temperatures in order to attain high diastereoselectivity in asymmetric reactions, were considered important factors in the search for the optimum conditions for the reduction of the α-bromoglycinate (48).

The minimum temperature at which the thermally initiated tin hydride reduction of α-bromoglycinates occurs is not certain. A way of ensuring that the reduction occurs at the lowest possible temperature, however, is to start the reduction at –78°C and allow the reaction mixture to warm up to room temperature very slowly. This was best achieved practically by simply commencing the reduction at dry ice/acetone temperature and allowing the entire set-up to equilibrate to room temperature overnight. Extension of the reaction time beyond sixteen hours did not improve the yield of the deuteriated product.

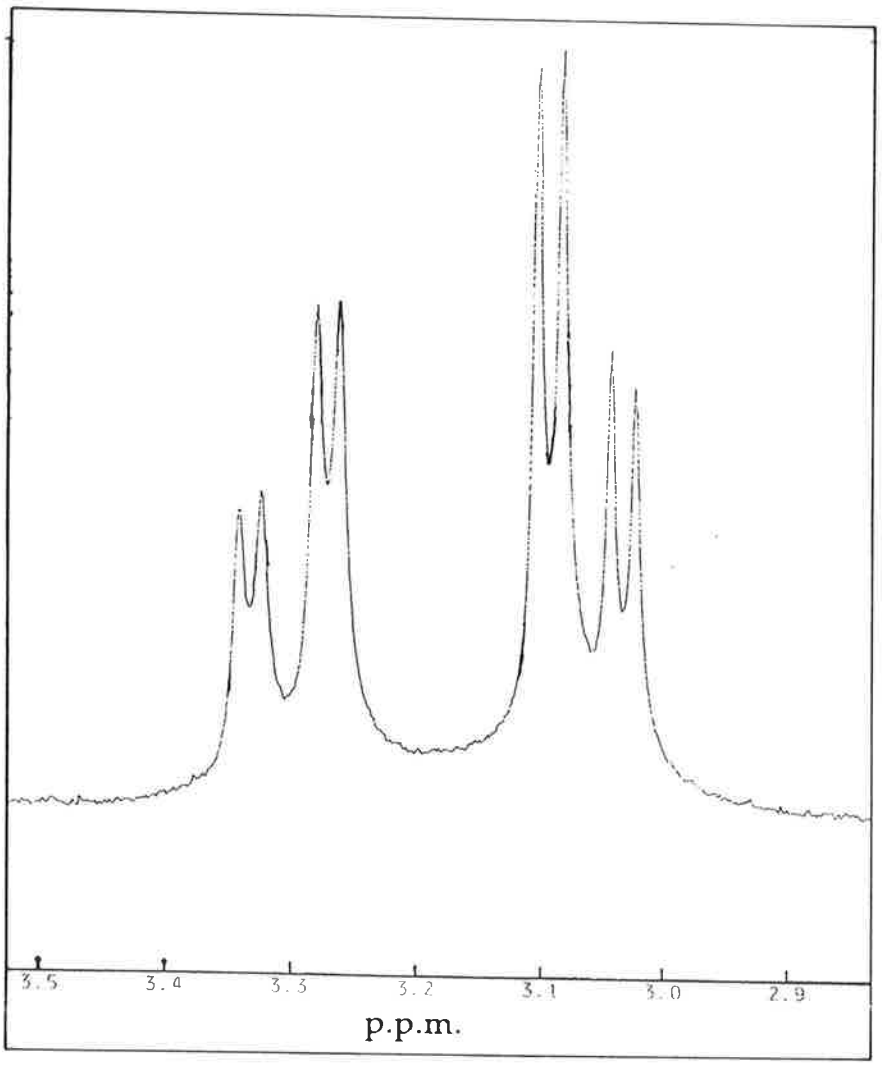


FIGURE 26

The reduction of the bromide (**48**) with tri-*n*-butyltin deuteride under these experimental conditions did indeed proceed with high diastereoselectivity. The α-deuteriated product obtained possessed a ^{1}H-N.M.R. spectrum identical to that of the parent α,α-diprotio compound (**47**), except for the α-proton region (δ 3.1 to 3.4), which formed the basis for calculating the d.e. of the radical reduction. The signals due to the diastereotopic α-protons of the parent compound are shown in **Figure 26**. This is the AB portion of an ABX system, with the X nucleus being the vicinal amide proton. The geminal coupling is 15.1 Hz, and the AX and BX couplings are 5.3 Hz and 5.9 Hz.

Monodeuteriation resulted in two diastereomeric products whose α-protons each gave separate doublet signals. Coupling only to the amide proton was observed, as geminal H-D coupling, though theoretically possible, was too small to be apparent. The major deuteriated diastereomer gave an α-proton doublet at δ 3.05 (J=5.4 Hz), whilst the α-proton of the minor deuteriated diastereomer resonated at δ 3.29 (J=4.7 Hz). Integration of each doublet enabled calculation of the d.e. for the reaction.

Although the two doublets of doublets due to the two diastereotopic α-protons of (**47**) were separated to baseline resolution in deuteriochloroform, at 300 MHz, problems were encountered when integration of the two multiplets revealed that the ratio of the area of the upfield doublet of doublets (centred at δ 3.05) to the area of the downfield doublet of doublets (centred at δ 3.29) was not 1:1, but rather *ca.* 1.04 : 1. It was thus apparent that an impurity which resonated under the upfield doublet of doublets was present, despite the analytical purity of the ester.

This is evident upon inspection of **Figure 26**. The double of doublets centred at δ 3.05 is distorted by the underlying signal due to the unknown impurity. Purification of the ester by preparative H.P.L.C. failed to remove this impurity, however, as evidenced by the integral ratio remaining at *ca.* 1.04 : 1.

When the spectrum of this compound was run in d_6-benzene at 300 MHz, however, the impurity now resonated as a distinct, broadened singlet at δ 3.14. In this solvent, the two doublets of doublets were situated at δ 3.34 and δ 3.22. Geminal coupling was 18.2 Hz. The downfield doublet of doublets exhibited a 5.5 Hz coupling to the amide proton, whilst the upfield doublet of doublets exhibited a 6.0 Hz coupling to this nucleus. Unfortunately, the chemical shift difference between the two α–proton signals was now only 0.12 p.p.m. (c.f. the 0.24 p.p.m. difference in deuteriochloroform), resulting in slight merging. This did not allow for the accurate integration of each multiplet. As a result, it was necessary to run the spectrum at the higher field of 500 MHz. Under these conditions, resolution of the two multiplets was now adequate, as shown in **Figure 27**.

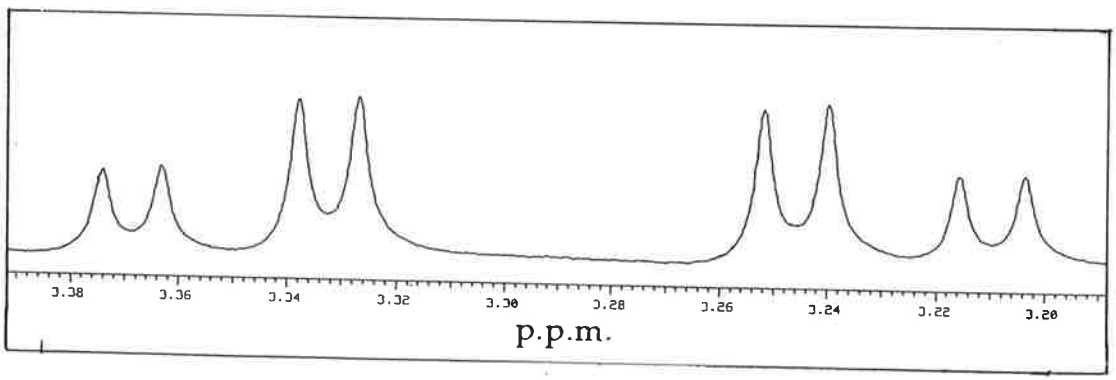


FIGURE 27

The ^{13}C-N.M.R. spectrum of the deuteriated product was identical to that of the parent compound, with the exception of the signal due to the α-carbon. This shifted upfield by *ca.* 0.2 p.p.m. (42.26 to 42.05 p.p.m.) upon deuteration, and now appeared as a 1 : 1 : 1 triplet (J=19.9 Hz) in the broad band decoupled spectrum. This is due to coupling of the α carbon nucleus to the deuterium nucleus, which possess a spin of unity.

As stated above, the α-proton of the major α-deuterio diastereomer resonated a lower field than that of the minor diastereomer. With knowledge of the magnetic shielding effect exerted by the phenyl group of the 8-phenylmenthyl moiety, this implied that the α-proton of the major diastereomer points towards the phenyl group. This implication arises from the expectation that the α-proton pointing towards the phenyl group would experience a greater magnetic shielding effect that its geminal partner, and hence will resonate at lower field. However, even when armed with this knowledge, it is impossible to tell whether the 2-(*S*) or 2-(*R*) diastereomer was formed in excess as the preferred conformation of the 8-phenylmenthyl *N*-*t*-Boc-glycinate was still unknown.

Due to the non-crystalline nature of the product, the only effective means of purification (i.e. removal of tin residues) was flash chromatography. It was necessary to carry this out twice, as residual tin by-products persisted after initial chromatography.

Reaction conditions such as solvent, temperature, concentration and the ratio of tri-*n*-butyltin deuteride to the α-bromoglycinate (**48**) were systematically varied in an effort to improve the diastereoselectivity of the reduction. These conditions, along with the experimental results, are summarized in **Table 7**.

	Bu_3SnD: (48) RATIO	CONC. (48) (mM)	SOLVENT	TEMP. (°C)	YIELD (%)	2-(*S*) : 2-(*R*)	d.e. (%)
1	1.1	70	ether	–78 °C → R.T.	85	84.5 : 15.5	69
2	1.1	128	ether	–78 °C → R.T.	71	90.5 : 9.5	81
3	2.0	245	ether	–78 °C → R.T.	70	95.0 : 5.0	90
4	2.0	490	ether	–78 °C → R.T.	60	94.0 : 6.0	88
5	2.0	245	toluene	–78 °C → R.T.	35	94.0 : 6.0	88
6	1.1	92	ether	R.T.	59	82.5 : 17.5	65
7	2.0	245	ether	R.T.	72	90.0 : 10.0	80
8	2.0	245	benzene	80 °C	41	69.0 : 31.0	38

TABLE 7

As can be seen, the diastereoselectivity of the reduction is markedly concentration and temperature dependent. Entries 1 and 2 (**Table 7**) show a 12% increase in d.e. upon doubling the concentration of both reactants. Roughly doubling the concentration of bromide, and quadrupling the concentration of stannane (Entry 3) resulted in the highest d.e. (90%) being observed. The α-proton region of the 500 MHz ^{1}H-N.M.R. spectrum of the product of this reaction is shown in **Figure 28**.

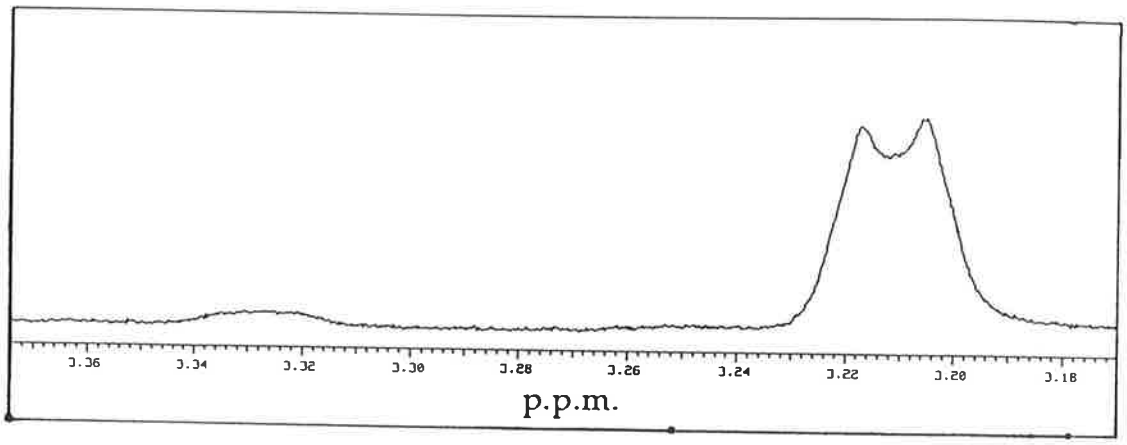


FIGURE 28

Further doubling of the concentration of both reactants (Entry 4) resulted in a d.e. of 88%, which, within experimental error, represents no significant change from Entry 3. Switching from ether to the much less polar toluene also made no significant change to the diastereoselectivity, although the chemical yield of deuterated product was dramatically lowered (Entry 5).

Running the reduction at room temperature in ether at low concentration with only 1.1 equivalents of deuteriostannane (Entry 6) lowered the d.e. substantially (to 65%). At the same temperature, but with two equivalents of deuteriostannane and at high concentration resulted in an improved d.e. of 80% (Entry 7). At still higher temperature (refluxing benzene, Entry 8) the d.e. was as low as 38%.

The concentration dependency of the diastereoselectivity can be accounted for if the following assumptions are made:-

1) The major α−deuterio diastereomer arises from delivery of a deuterium atom to the α-centred radical (**120**) whilst the radical is still in

the same conformation as when it was first generated (by carbon-bromine bond homolysis).

2) Increasing the concentration of tri-*n*-butyl deuteride shortens the lifetime of the α-centred radical. The simple rate law $k \propto [R^{\bullet}].[n\mathrm{Bu_3SnD}]$, which states that the rate of consumption of the radical is directly proportional to the stannane concentration, indicates that the assumption is valid.

If these two assumptions hold true, then increasing the tri-*n*-butyltin deuteride concentration increases the rate at which the major, first-formed conformer of the radical (**120**) is scavenged by deuterium. Put simply, the major conformer is reduced before it has time to adopt the alternative conformer whose reduction produces the minor α-deuterio diastereomer.

The temperature dependence of the diastereoselectivity can be explained in a more straightforward manner. Given that there are thermal rotational barriers between the various conformers of the α-centred radical (**120**), a decrease in the reaction temperature will tend to restrict the conformational mobility of the open chain. This effect is manifested in a product of high diastereomeric purity. Conversely, increasing the reaction temperature increases the population of the minor rotamer, giving rise to a product of low diastereomeric purity.

Hydrolysis of the 95:5 mixture of α-deuterio diastereomers was next attempted. The purpose of this was twofold. Firstly, it was important to show that the ester could be hydrolyzed to the free amino acid without loss of deuterium. Secondly, the free amino acid was needed in order to

synthesize a derivative which would enable assignment of the configuration of the α-centre.

The conditions developed for the non-racemizing hydrolysis of 8-phenylmenthyl *N*-*t*-Boc-alaninate (**74a**) were used. The α-deuterioglycinate was dissolved in neat trifluoroacetic acid, and fifteen minutes later a twofold volume of 6N HCl was added. Sixteen hour reflux gave the crude (*S*)-2-deuterioglycine hydrochloride, which was converted to the free zwitterion (**132**) by ion exchange chromatography. The overall yield for this process was 95%. The melting point of the pure amino acid was 235-236°C, which compared favourably with the reported value of 234°C.[92] The ^{1}H-N.M.R. spectrum of (**132**), run in D_2O, consisted of a 1:1:1 triplet centred at δ 3.53. The coupling constant was too small to be measured accurately, but an estimation of *ca.* 2 Hz was made. The reported[11] chemical shift was δ 3.65. However, the internal reference standard and coupling constant were not quoted in this publication. Thus, comparison with the values reported here could not be made. The internal reference standard utilized here was 3-(trimethylsilyl)-1-propane-sulphonic acid sodium salt. Analysis of the 2-deuterioglycine by mass spectrometry indicated that little or no deuterium had been lost in the hydrolysis step.

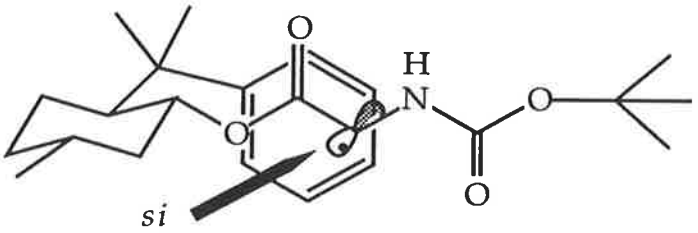
2.2 STEREOCHEMICAL ASPECTS OF THE α-CENTRED RADICAL (120)

The free 2-deuterioglycine (**132**) was converted to its methyl ester/*N*-camphanamide (**129**). The chemistry used differed from the method reported by Armarego[92], which involved amidation of the amino acid with camphanoyl chloride[93], followed by methylation of the resultant acid with diazomethane. The method reported here was considered to be more expedient. Treatment of the amino acid (**132**) with methanolic hydrogen chloride was followed by amidation with camphanoyl chloride (from camphanic acid monohydrate and thionyl chloride[93]) under Schotten-Baumann conditions. This gave the glycine derivative (**129**) in a modest yield of 55%, but in sufficient quantity for ^{1}H-N.M.R. analysis.

The ^{1}H-N.M.R. spectrum (300 MHz) was consistent with the spectral data reported for this compound by Armarego[92], who utilized a 60 MHz spectrometer. Due to the higher field instrument used here, more detail was evident in the spectrum of (**129**). At 60 MHz, the protons of the geminal methyl group attached to C-7' resonated as one signal at δ 1.12. At 300 MHz, the signal resolved into two peaks at δ 1.123 and δ 1.105.

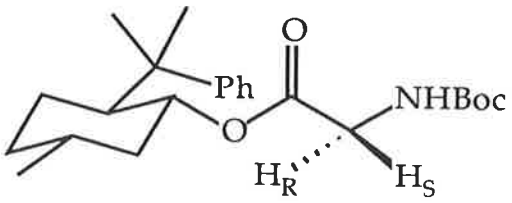
At 60 MHz, Armarego found it necessary to utilize the shift reagent Eu(dpm)$_3$ to increase the separation of the two doublets centred at δ 4.03 and δ 4.13 (due to the two diastereotopic α-protons) in order to measure the integral of each proton. In this case, at 300 MHz, this was not necessary. The pro-(*S*) proton resonated at δ 4.172, whilst the pro-(*R*) proton resonated at δ 3.982, with the two peaks being baseline resolved. The predominance of the doublet signal at δ 4.172 indicated that the amino acid had the (*S*) configuration. As both the chiral glycine ester (**128a**) and the bromide (**48**) are produced by delivery of deuterium and bromine

respectively.to the same α-centred radical (**120**), it is very probable that the configuration at the α-carbon of the bromide is also (*S*). With the absolute stereochemistry of the 2-deuterioglycinate (**128a**) now known, a transition state model for the deuteriation of the α-centred radical (**120**) could now be proposed. This model is shown in **Figure 29**. Adoption of the configuration shown, followed by delivery of deuterium to the *sinister* face of the radical (the face opposite the phenyl group) accounts for the 2-(*S*) stereochemistry of the reduction product.

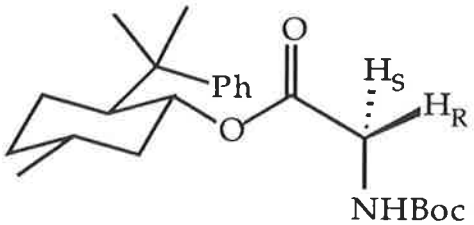


(**120**)

FIGURE 29



(Z)-rotamer (**47a**)



(*E*)-rotamer (**47b**)

FIGURE 30

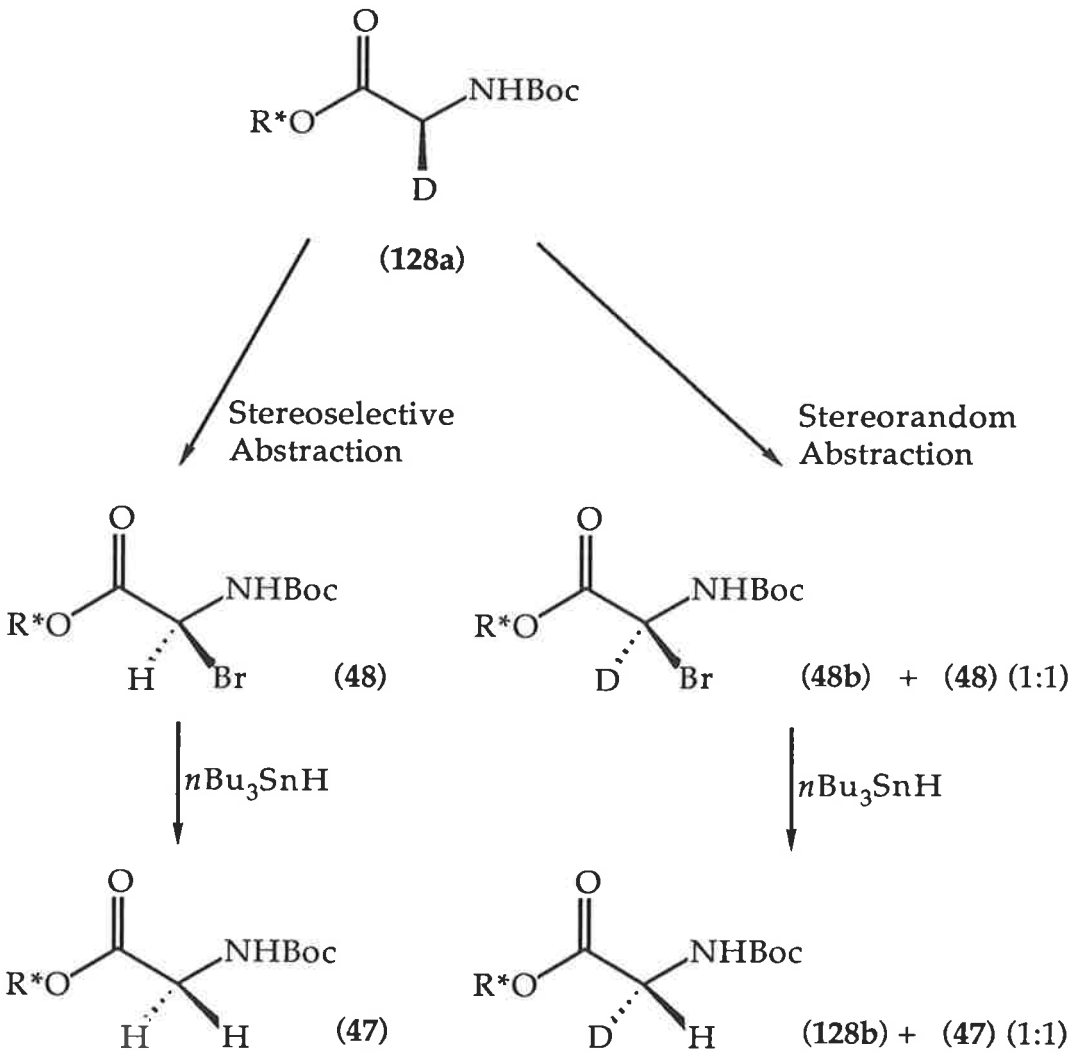
Assignment of the 2-(*S*) configuration to the major 2-deuterioglycinate (**128a**), in turn, allows for the assignment of the doublet of doublets centred at δ 3.29 in the ^{1}H-N.M.R. spectrum of the undeuteriated compound (**47**), as being due to the pro-(*S*) proton. When drawn as the Z-rotamer (**47a**) (**Figure 46**), the pro-(*S*) proton points away from the phenyl ring of the 8-phenylmenthyl moiety. This is consistent with the

observation that the pro-(*S*) proton resonates downfield of the pro-(*R*) proton, since the pro-(*R*) proton would be expected to experience greater magnetic shielding than the pro-(*S*) proton. These observations indicate that the *Z*-rotamer (**47a**) is preferred over the *E*-rotamer (**47b**).

It was subsequently of interest to investigate the selectivity of α-hydrogen abstraction from (**47**) by bromine atom. Since the *Z*-rotamer appeared to be predominant, we speculated that the pro-(*S*) hydrogen, which points away from the phenyl group in this conformation, may be stereoselectively removed in the bromination reaction.

It was apparent that this problem could be solved by brominating a sample of the (*S*)-2-deuterioglcinate (**128a**) with *N*-bromosuccinimide. If the hydrogen atom abstraction was face selective, deuterium would be removed completely, leading to the completely undeuteriated bromide (**48**). At the other extreme, stereorandom hydrogen atom abstraction would lead to a 1:1 mixture of the bromide (**48**) and the deuteriated bromide (**48b**) (**Scheme 28**).

8-phenylmenthyl *N*-*t*-Boc-2-deuterioglycinate (**128a**) was brominated with *N*-bromosuccinimide under standard conditions. In order to produce a stable derivative for analysis, the resultant bromide was immediately reduced with tri-*n*-butyltin hydride in ether from −78°C to room temperature (i.e., under the optimum stereoselective reduction conditions). If deuterium had been selectively removed in the bromination step, the product of reduction with tri-*n*-butyltin hydride would be the undeuteriated ester (**47**) (**Scheme 28**). A non-selective hydrogen abstraction would lead to a 1:1 mixture of (**48**) and the 2-(*R*)-deuterioglycinate (**128b**).



SCHEME 28

Mass spectral analysis of the reduction product indicated that the $d_0 : d_1$ ratio was 73 : 27, indicating that the bromination step removed three times as much deuterium as protium. The α-proton region of the ^{1}H-N.M.R. spectrum of the reduction product (300 MHz, $CDCl_3$) is shown in **Figure 31**. As is evident, the pattern is very similar to that of the authentic undeuteriated compound (**47**), indicating that (**47**) is the major species present. Subtraction of the spectrum of (**47**) from the spectrum of the reduction product left a doublet centred at δ 3.29. This doublet was due to

the α-proton of the 2-(*R*)-deuterioglycinate (**128b**), as a later experiment (to be discussed shortly) showed. The presence of (**128b**) was consistent with the expectation that stereoselective reduction of the deuteriated bromide (**48b**) with tri-*n*-butyltin hydride would place hydrogen in the pro-(*S*) locus (**Scheme 28**).

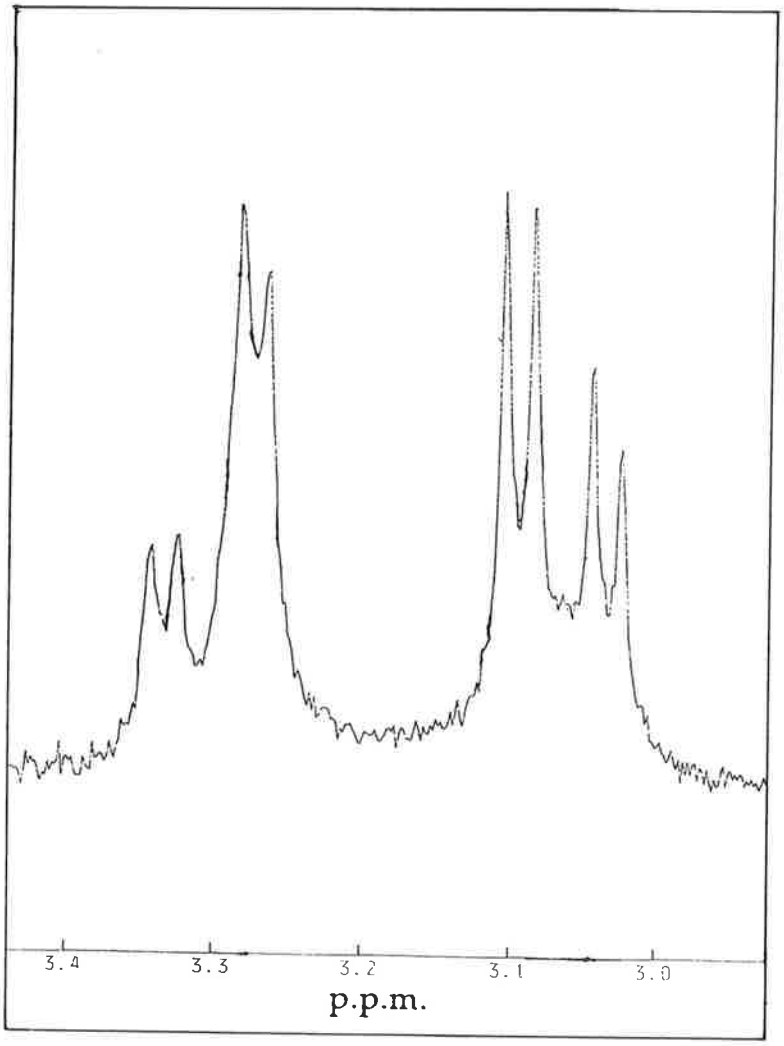


FIGURE 31

Easton and Hay[36] have reported that a kinetic isotope effect ($k_H/k_D = 3.15$) in the bromination of similar (achiral) glycinates with *N*-bromosuccinimide. Were it not for this kinetic isotope effect, the selectivity for the pro-(*S*) hydrogen of (**128a**) may be even higher.

The selectivity for the 2-(*S*) deuterioglycinate (**128a**) raised the question of why the inferred conformation (ester carbonyl and C-N bond *syn*) was preferrentially adopted by the α-centred radical (**120**). In addition, the high level of asymmetric induction indicated that this conformation was of significantly lower energy than the alternative *anti* conformation. The question of why this should be so needed to be addressed.

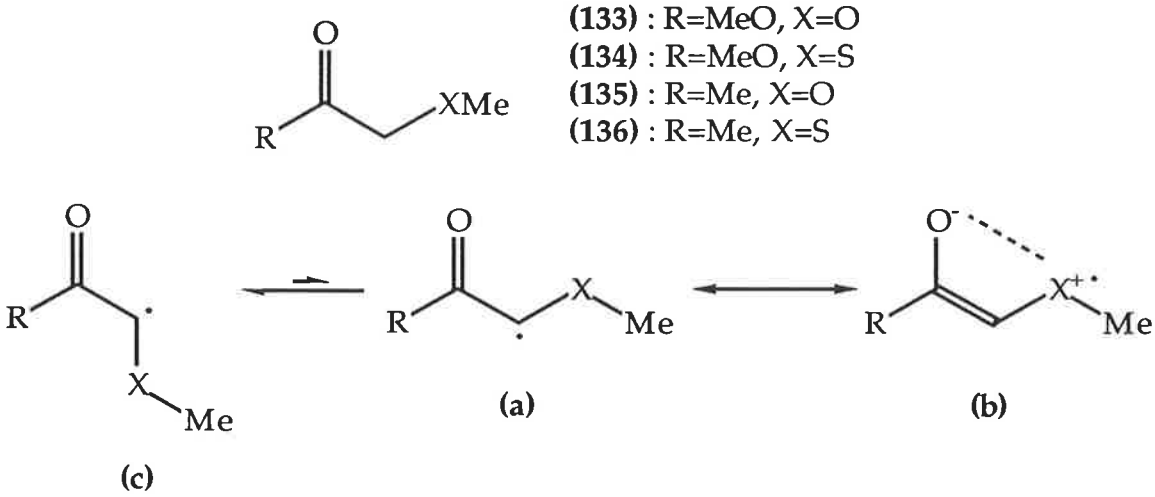


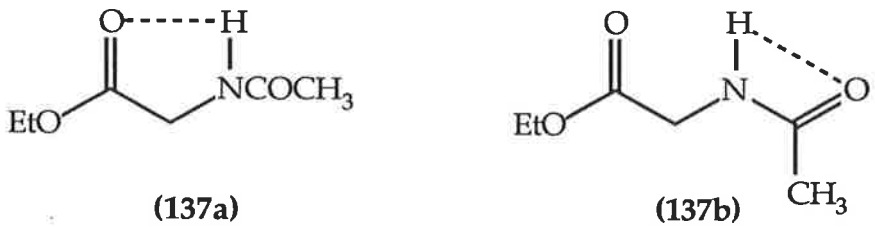
FIGURE 32

Beckwith and Brumby[94] studied the Electron Spin Resonance spectra of the capto-dative free radicals (**133a**) - (**136a**) (**Figure 32**). These radicals were derived from compounds (**133**) - (**136**) through hydrogen atom abstraction by the *t*-butoxyl radical at the position α to both the carbonyl group and the heteroatom. The authors interpreted the E.S.R. spectra of these radicals to show that they exist in two distinct conformations, with one of the conformers predominating.

Taking into account their semi-empirical molecular orbital calculations at the M.N.D.O. level of approximation, the authors concluded that the two rotamers observed were (**a**) and (**c**) (**Figure 32**) and that (**a**) is the

predominant radical. These results clearly show that the *Z* rotamer is favoured in capto-dative radicals of this type.

Alternatively, hydrogen bonding may be responsible for the conformational rigidity of the capto-dative radical. The hydrogen bond in question is between the amide hydrogen and ester carbonyl oxygen. One would expect this to be the preferred hydrogen bond since resonance within the ester group renders the carbonyl oxygen more basic than the alkoxy oxygen. The resonance contributor (**37**) to the α-centred radical (**34**) (**Figure 7**, Chapter 1-Introduction) could add to this effect.



(137a) **(137b)**

FIGURE 33

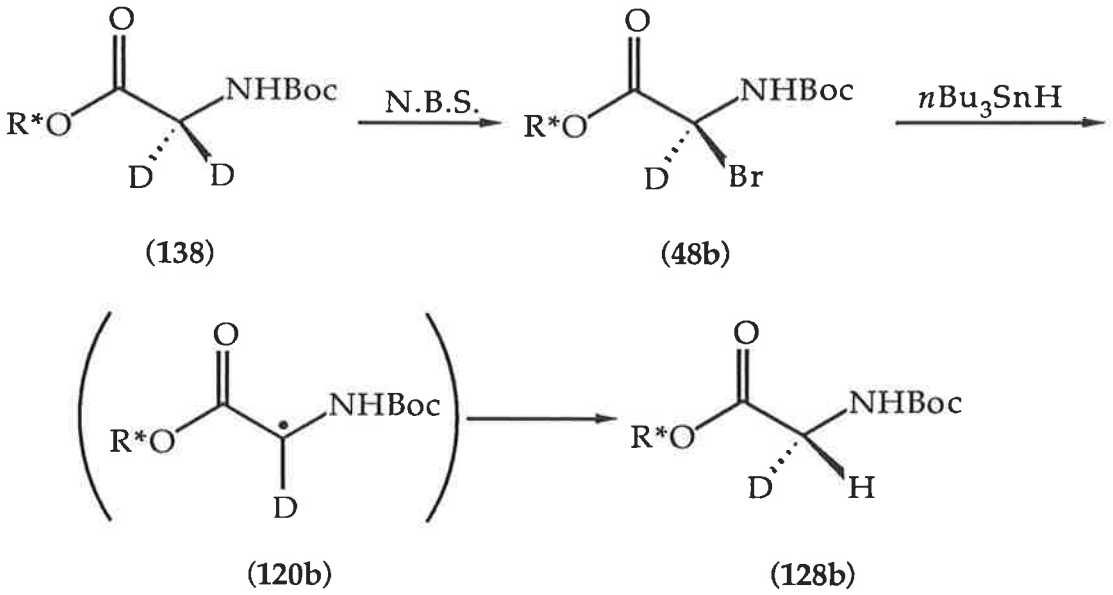
Slet[95] examined the I.R. spectra of *N*-acetylglycine ethyl ester in carbon tetrachloride solution and deduced that intramolecular hydrogen bonding between the amide hydrogen and ester carbonyl oxygen was occurring (**Figure 33**, structure **137a**)). The enthalpy of formation of this hydrogen bond was calculated to be -3.55 kJ.mol^{-1}, indicating a relatively weak interaction. However, the the resonance effect discussed above could foreseeably increase the basicity of the ester carbonyl oxygen of the radical (**120**) utilized in our study. This, in turn, would make the hydrogen bond significantly stronger, accounting for the preference for the (*Z*)-radical over the (*E*)-radical.

A previous publication by Slet[96] casts an ambiguous light on these later findings. N.M.R. and I.R. spectroscopy indicated that *N*-acetylglycine ethyl ester in carbon tetrachloride forms an intramolecular hydrogen bond (with a -18.4 kJ.mol^{-1} enthalpy of formation) between the amide hydrogen and amide oxygen (**Figure 33**, structure **137b**)). It is unclear whether this means that both types of hydrogen bonding occur in *N*-acylamino esters, or whether the later report is to be taken as a correction of the earlier report.

Irrespective of the reason for the high conformational rigidty of the α-centred radical (**120**), the results of this study show that this radical allows for the synthesis of (*S*)-2-deuterioglycine of high enantiomeric purity.

2.3 8-PHENYLMENTHYL *N*-*t*-BOC-(*R*)-2-DEUTERIOGLYCINATE (128b)

It became apparent that the methodology used to produce (*S*)-chiral glycine (**132**) could be used to synthesize (*R*)-2-deuterioglycine, not by use of the enantiomeric chiral auxiliary, but by simply interchanging the roles of hydrogen and deuterium. This entailed bromination of the α,α-dideuterioglycine derivative (**138**), followed by low temperature reduction of the bromide (**48b**) with tri-*n*-butyltin hydride.



R* = 8-phenylmenthyl

SCHEME 29

Accordingly, commercially available 2,2-dideuterioglycine was converted to its *N*-*t*-Boc derivative (**139**), which was subsequently coupled with 8-phenylmenthol under standard conditions. Bromination of the product (**138**) was accomplished by the same method as that used for the α,α-diprotio analogue (**47**). The reduction step involved exactly the same conditions as those employed previously in obtaining the (*S*)-chiral

glycinate (**128a**) in 92% d.e. (**Table 7**, Entry 3). 500 MHz ^{1}H-N.M.R. analysis of the product so obtained revealed that, as expected, the high field doublet (due to the pro-(*S*) proton) now predominated over the low field doublet (due to the pro-(*R*) proton), as indicated by **Figure 34**. However, the spectrum indicated that a significant amount of undeuteriated material was also present. Mass spectroscopic analysis confirmed this. Analysis of the peaks at m/z 389, 390 and 391 revealed that the d_1 : d_0 ratio was *ca.* 95:5.

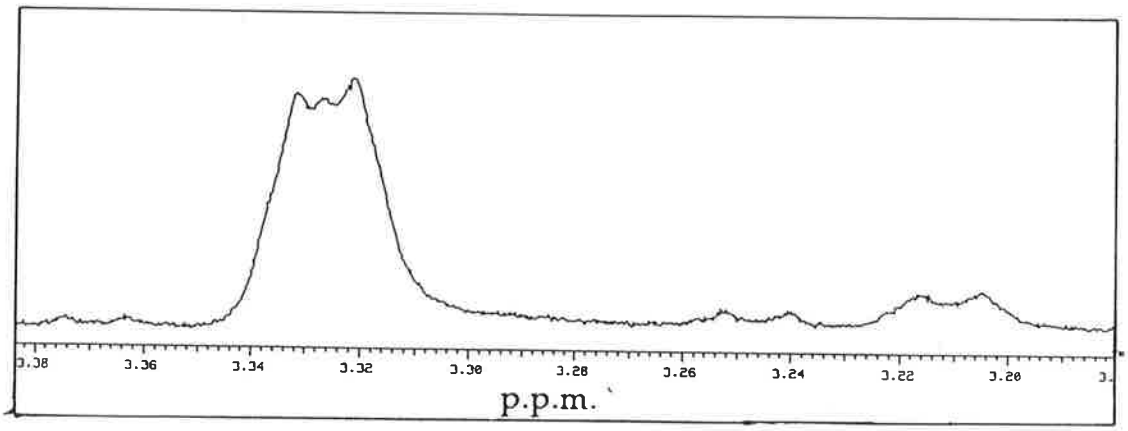


FIGURE 34

The presence of undeuteriated material made accurate determination of the d.e. for this reaction difficult. However, integration of the α-proton region yielded a 2-(*R*) : 2-(*S*) ratio of 89 : 11. This represents an apparent d.e. of 78%, but the actual d.e. must be significantly higher. There is no apparent reason why the inherent diastereoselectivity of the reduction of the deuteriated radical (**120b**) with tri-*n*-butyltin hydride should be lower than that for reduction of the undeuteriated radical (**120**) with tri-*n*-butyltin deuteride. To estimate the true d.e. of the 2-(*R*) compound (**128b**), the deuterium content of the product (95%) must be taken into account. Subtracting the contribution made by the 5% of undeuteriated material to the integrals of the pro-(*S*) and pro-(*R*) signals in the ^{1}H-N.M.R. spectrum alters the 89 : 11 ratio to 84 : 6, which is equivalent to

a *ca.* 93 : 7 2-(*R*) : 2-(*S*) ratio. Hence the actual d.e. of the 2-(*R*) 2-deuterioglycinate (**128b**) is , in all likelihood, closer to 90% (the d.e. value of the (*S*)2-deuterioglycinate obtained under optimum conditions) than the ^{1}H-N.M.R. spectrum of this product would indicate.

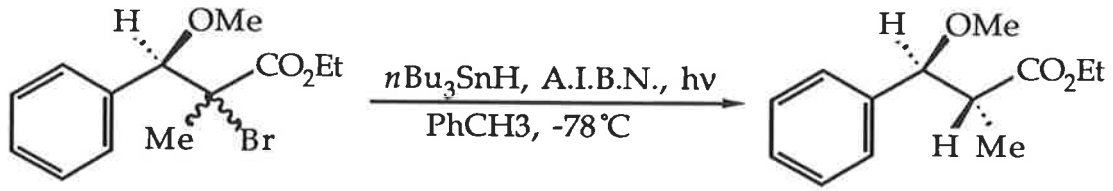
The low deuterium content of the reduced product (**128b**) was unexpected, as the 2,2-dideuterioglycine from which it was ultimately derived was 98 atom % deuteriated. This prompted close investigation of the deuterium content of *N*-*t*-Boc-2,2-dideuterioglycine (**139**) and its 8-phenylmenthyl ester (**138**). The mass spectrum of the acid indicated a 97 : 2.5 : 0.5 d_2 : d_1 d_0 ratio, indicating that little or no deterium was lost in the tertiarybutylcarbonylation of the amino acid. The mass spectrum of the ester, however, revealed a 92 : 8 d_2 : d_1 ratio, indicating the loss of some deuterium during esterification of (**139**) with (–)-8-phenylmenthol. The α-proton region of the ^{1}H-N.M.R. spectrum of the ester (**138**) contained low intensity signals at δ 3.29 (0.03 H, pro-(*S*) H) and δ 3.05 (0.05 H, pro-(*R*) H). This accounted for the 8% content of monodeuteriated ester indicated by mass spectroscopy.

The preferential exchange of the pro-(*R*) deuterium atom is difficult to rationalize in light of the *si* face selectivity demonstrated by this system in the reactions described in this thesis. However, it must be appreciated that deuterium/hydrogen exchange would involve an enol or enolate intermediate. The preferred conformation, and hence the diastereofacial selectivity of such a charged species may well differ from the confomation of the iminoacetate (**49**) and the α-centred radical (**120**).

The near-selective deuterium abstraction demonstrated in the bromination of the (*S*)-2-deuterioglycinate (**128a**) would be expected to

remove nearly all of the 3% pro-(*S*) protium and leave most of the 5% pro-(*R*) protium. Hence the intermediate α-centred radical (**120b**) would be only 95% deuteriated. Reduction with tri-*n*-butyltin hydride then gives the 95 : 5 mixture of deuteriated and undeuteriated products detected by mass spectroscopy.

2.4 STEREOSELECTIVE REDUCTION OF ACYCLIC RADICALS WITH TRI-*n*-BUTYLTIN HYDRIDE - A LITERATURE REPORT



(140) **(141)**

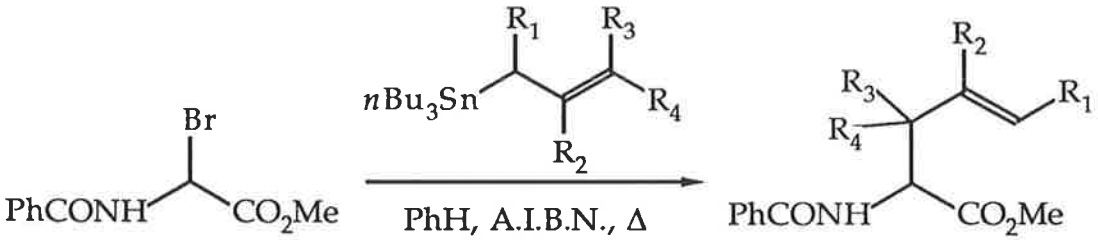
SCHEME 30

During the course of this work, literature reports of asymmetric induction at radical sites in acyclic systems began to appear. Guindon and co-workers[97] reported the reduction the α-bromo ester (**140**) with tri-*n*-butyltin hydride at low temperature (**Scheme 30**). The high threo selectivity was attributed to the intermediate acyclic radical adopting either conformation **1** or **2** (**Figure 35**), both of which favour approach of the stannane to the *rectus* face, giving the 2-(*R*) stereochemistry observed for (**141**).

CONFORMATION 1 **CONFORMATION 2**

FIGURE 35

Conformation **1** would arise from the interaction of the semi-occupied molecular orbital with the lowest unoccupied molecular orbital of the neighbouring C-O bond. In conformation **2**, the intramolecular dipole-dipole interactions between the two vicinal electronegative groups are minimized by adoption of the *anti* orientation.

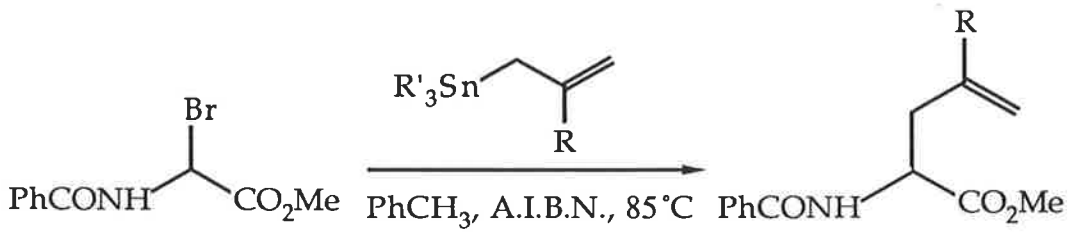


(142) **(143)**

a) $R_1 = R_2 = R_3 = R_4 = H$
b) $R_1 = R_3 = R_4 = H$, $R_2 = Me$
c) $R_1 = R_2 = R_3 = H$, $R_4 = Me$
d) $R_1 = Me$, $R_2 = R_3 = R_4 = H$
e) $R_1 = R_2 = H$, $R_3 = R_4 = Me$

EASTON *et al.*

SCHEME 31



(142) **(144)**

a) R= CO_2Et, R'= *n*Bu
b) R= CN, R'= *n*Bu
c) R= Cl, R'= *n*Bu
d) R= H, R'= Ph

BALDWIN *et al.*

Having observed that the α-centred radical (**120**) undergoes highly stereoselective reduction with tri-*n*-butyltin deuteride, elaboration of the bromide (**48**) by other suitable radicalophiles will be studied. It is envisaged that the α-centred radical (**120**) should also undergo carbon-carbon bond forming reactions with allyltri-*n*-butylstannanes. The radical chain "allyltransfer" reaction of allylstannanes has been developed into syntheses of amino acids independently and concurrently by the research groups of Easton[85,98] and Baldwin[99]. These workers showed that the α-bromoglycine derivative (**142**) underwent AIBN initiated reaction with

the allylstannanes shown in **Scheme 31** to give the α-allylglycine derivatives **(143)** and **(144)** in fair yields. This reaction proceeds through the radical chain mechanism shown in **Figure 36**.

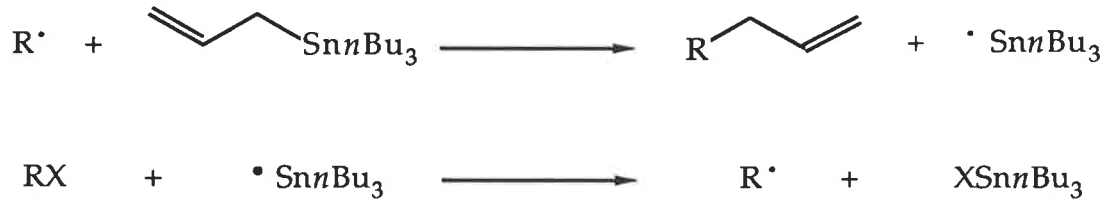
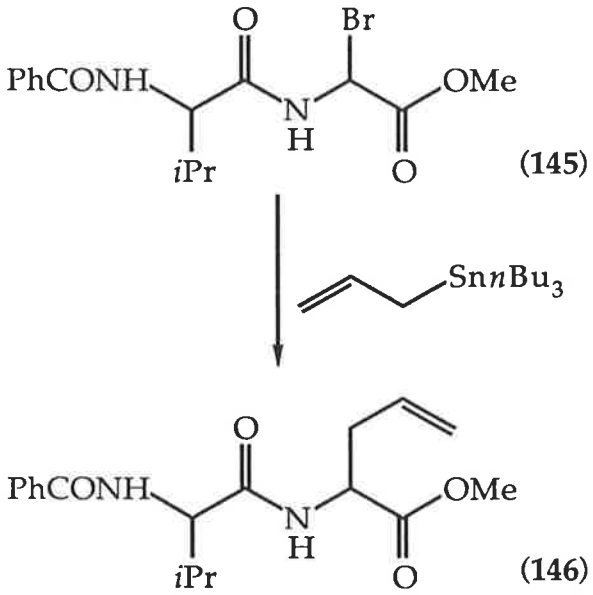


FIGURE 36

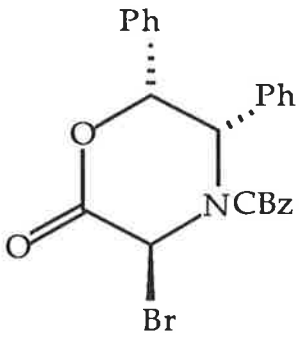


SCHEME 32

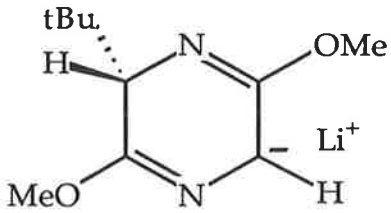
It is worth noting that Easton *et al* extended this work to asymmetric α-amino acid synthesis[85]. Treatment of the brominated dipeptide **(145)** gave the allyl substituted product **(146)** as a 3:1 mixture of diastereomers (**Scheme 32**). The use of the more efficient chiral auxiliary, 8-phenylmenthol, should give a higher d.e. Thus treatment of the

bromide (48) with allylstannanes should give 8-phenylmenthyl *N*-*t*-Boc-allylglycinates in high diastereomeric purity.

γ-δ-unsaturated amino acids are of interest, not only due to the synthetic utility of the double bond, but also due to their action as "suicide substrate" inactivators of pyridoxal phosphate dependent enzymes[100]. Naturally, it would be beneficial for studies of enzyme inactivation to involve the use of enantiomerically pure α-allyl-α-amino acids. The electrophilic asymmetric glycine template (**147**) of Williams[33] and the nucleophilic asymmetric glycine template (**148**) of Schollkopf[12] (**Figure 37**) both provide allylglycine and its derivatives in high enantiomeric purity.



(147)



(148)

FIGURE 37

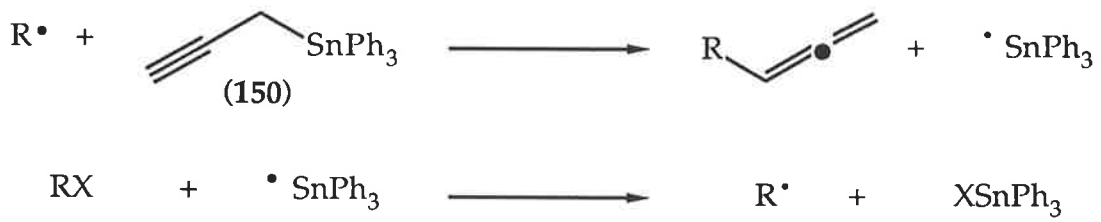
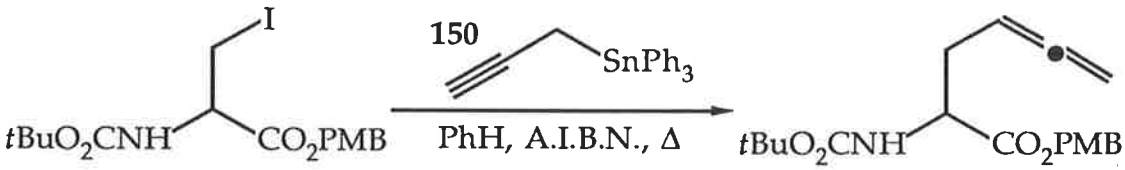


FIGURE 38

Another radicalophile which should be suitable for elaboration of the bromide (**48**) is propargyl triphenylstannane (**150**). This reagent has been

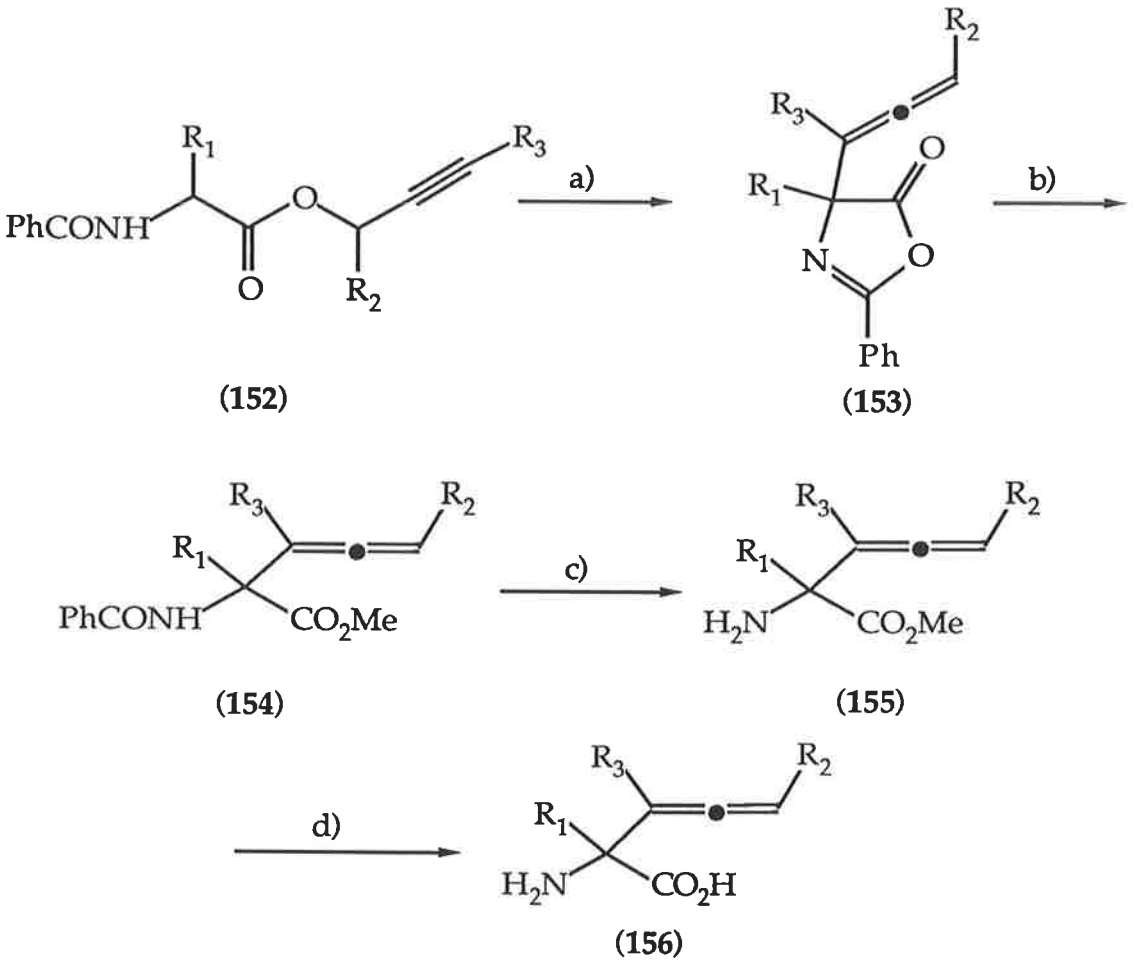
reported by Baldwin[101] to undergo "allene transfer" reactions with alkyl radicals. This reaction proceeds through the radical chain mechanism shown in **Figure 38**. Among the alkyl radicals employed was the β-iodoalanine derivative (**149**), giving the corresponding β-allenyl derivative (**151**) (**Scheme 33**). Of course, the application of this methodology to the α-bromoglycinate (**48**) will yield α-allenyl-α-amino acids.



(**149**) (**151**)

SCHEME 33

Castelhano, Krantz and co-workers[37] have developed a racemic synthesis of α-substituted α-allenyl-α-amino acids by Claisen rearrangement of the α-benzamido propargylic esters (**152**). They have shown that the α-substituted α-allenyl-α-aminoacids (**156**) derived from the process outlined in **Scheme 34** are potent inactivators of Vitamin B_6 linked amino acid decarboxylases[102]. To date, however, the asymmetric synthesis of α-allenyl-α-amino acids has not been reported.



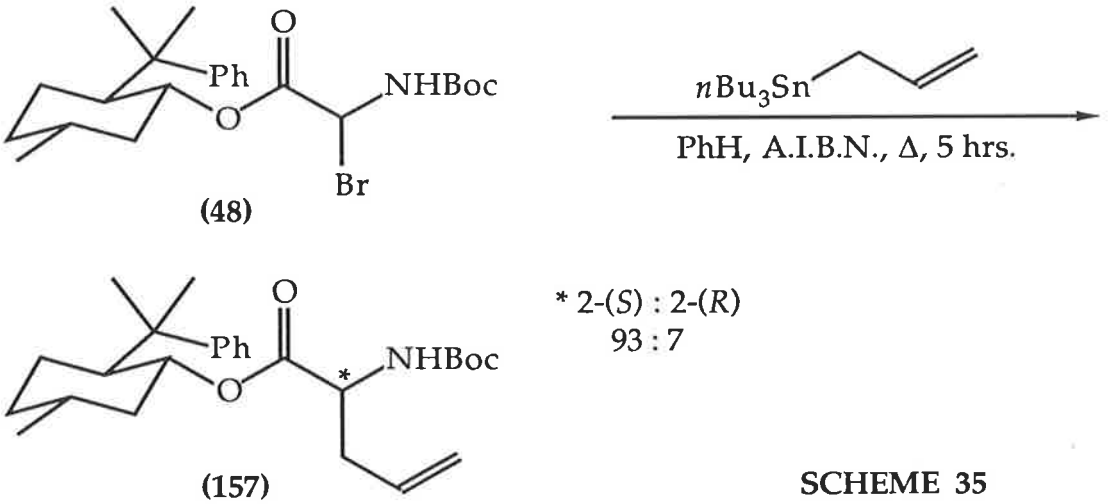
a) Ph_3P, CCl_4, NEt_3, CH_3CN; b) MeOH, NEt_3;
c) i) $Et_3O^+BF_4^-$, CH_2Cl_2 ii) 10% HOAc;
d) 1.0 M NaOH/MeOH

SCHEME 34

Chapter 3 - Results and Discussion

3.1 ALLYL TRANSFER TO THE BROMIDE (48)

The conditions described by Easton and Scharfbillig[98] for the allyl transfer reaction of allyl tri-*n*-butyltin with methyl *N*-benzoyl-2-bromoglycinate (**142**) were employed in the analogous reaction with 8-phenylmenthyl *N*-*t*-Boc-2-bromoglycinate (**48**). This involved treatment of the bromide (**48**) with two equivalents of commercially available allyl tri-*n*-butyltin and a catalytic amount of A.I.B.N. (5 mole %) in dry benzene at reflux for five hours.



(48)

(157)

* 2-(*S*) : 2-(*R*)
93 : 7

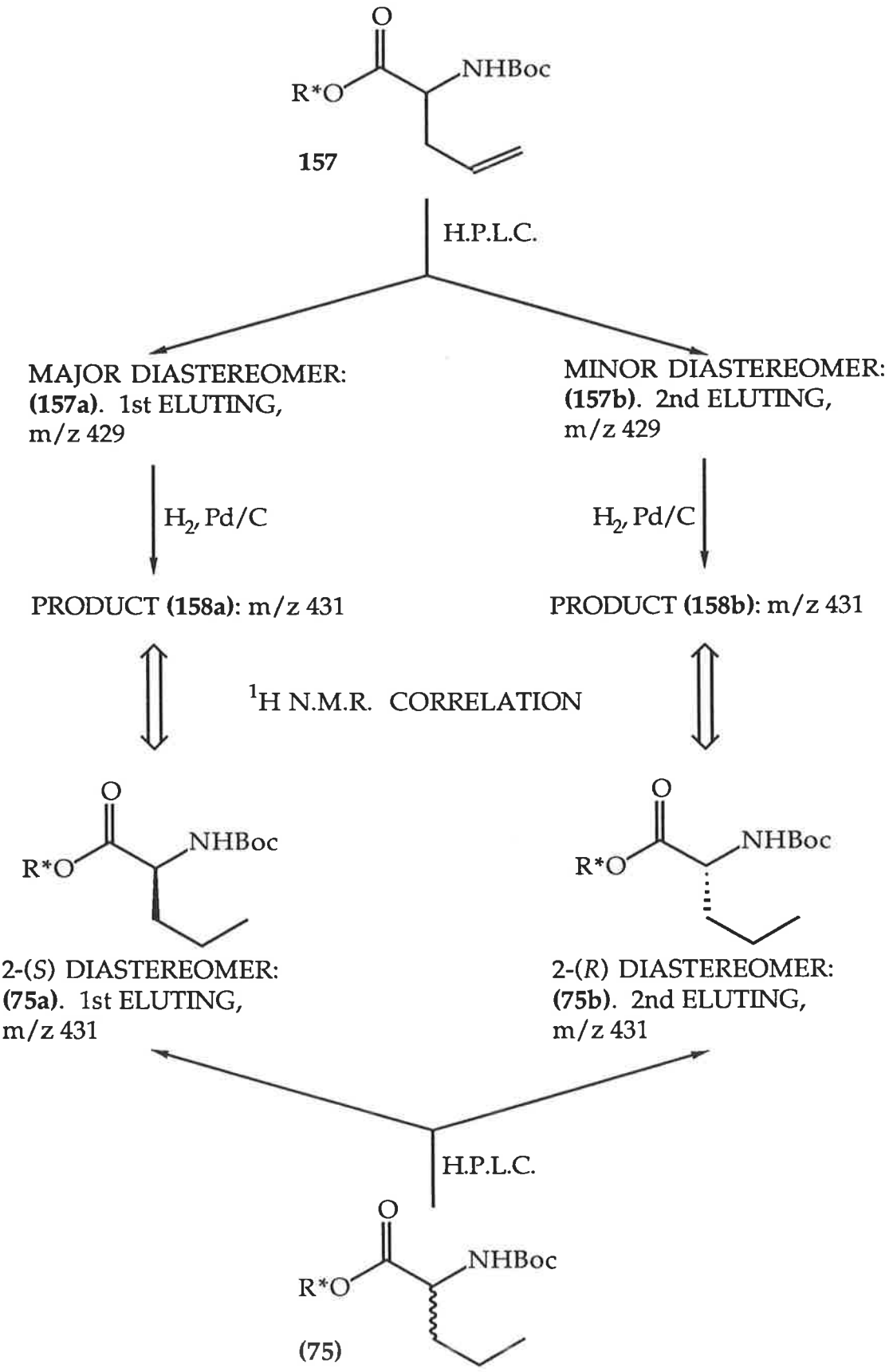
SCHEME 35

Under these conditions, allyl transfer to the bromide (**48**) occurred, giving the corresponding allylglycine derivative (**157**) in 76% yield as a 93:7 mixture of diastereomers (**Scheme 35**), after chromatographic removal of tin residues and low R_f impurities (probably resulting from decomposition of the bromide (**48**)). This yield compared favourably with that reported by Easton and Scharfbillig[99] (63% for *N*-benzoyl-(*R*,*S*)-allylglycine methyl ester (**143a**)).

As was observed for the diastereomeric products resulting from Grignard addition to the bromide (**48**), the major diastereomer produced was the more chromatographically mobile (i.e., higher R_f by T.L.C. and first eluting by H.P.L.C.) of the two. This strongly inferred that the major diastereomer possessed the 2-(*S*) stereochemistry, based on the correlation made earlier between the C-2 stereochemistry of *N*-*t*-Boc-amino acid 8-phenylmenthyl esters and their chromatographic behaviour.

The two diastereomeric allylglycine derivatives (**157a**) and (**157b**) were isolated by preparative H.P.L.C. and their ^{1}H-N.M.R. spectra were found to be identical to the fully characterized, authentic compounds (**79a**) and (**79b**), derived from (*R*,*S*)-allylglycine. Catalytic hydrogenation of the two separated diastereomers from the allyl transfer reaction gave the saturated compounds (**158a**) and (**158b**), whose 300 MHz ^{1}H-N.M.R. spectra were identical to those of the authentic norvalinates (**75a**) and (**75b**). As dicussed in Chapter 1, the first-eluting norvaline-derived diastereomer (**75a**) was proven to be the 2-(*S*) diastereomer by spectral comparison with authentic 8-phenylmenthyl *N*-*t*-Boc-2-(*S*)-norvalinate synthesized from (*S*)-norvaline. The 2-(*S*) diastereomer (**75a**) also had an identical ^{1}H-N.M.R. spectrum to the product obtained from hydrogenation of the major 8-phenylmenthyl *N*-*t*-Boc-allylglycinate diastereomer (**157a**), unequivocally showing that the allyl transfer reaction favours production of the 2-(*S*) diastereomer. These correlations are depicted diagramatically in **Scheme 36**.

Alternatively, the 93:7 mixture of diastereomers (**157**) was hydrogenated and the diastereomeric saturated products were shown to co-elute by H.P.L.C. with the authentic mixture of diastereomers (**75a**) and (**75b**).



R*= 8-phenylmenthyl

SCHEME 36

Both the major 8-phenylmenthyl *N*-*t*-Boc-allylglycinate diastereomer (**157a**) from the allyl transfer reaction and the major 8-phenylmenthyl *N*-*t*-Boc-2-deuterioglycinate (**128a**) from the deuteration reaction possessed the 2-(*S*) configuration. This was not unexpected as both products result from approach of a radicalophile to the same α-centred radical (**120**), and there is no good reason to assume that the radical should adopt different conformations for the two reactions. Therefore, the same arguments put forward to rationalize the stereochemical course of the deuteration reaction may be used for the analogous homolytic allylation reaction. That is, the capto-dative radical (**120**) adopts the *Z* geometry and is selectively attacked at the *sinister* face by the approaching allyl tri-*n*-butylstannane.

As discussed earlier, the level of diastereoselectivity in the reduction of the bromide (**48**) with tri-*n*-butyl deuteriostannane was found to vary with reaction temperature and absolute concentration. Hence, the effect of these two factors on the diastereoselectivity of the allylation reaction of the bromide (**48**) was also investigated. The results of this study are summarized in **Table 8**.

Quadrupling both the bromide and stannane concentrations gave the 2-(*S*) and 2-(*R*) allylglycine derivatives in a 92 : 8 ratio in refluxing benzene (Entry 2). Within experimental error, this result is not significantly different from that observed in the initial, less concentrated reaction (Entry 1; 2-(*S*):2-(*R*) = 93 : 7). This is in contrast with the deuteration reaction, where a doubling alone of the reactant concentrations improved the d.e. by 12%, though this effect was observed at a lower temperature in ether.

ENTRY	CONC. (48) (mM)	TEMP. (°C)	YIELD (157) (%)	D.E. (157) (%)
1	66	80	76	86
2	288	80	78	84
3	66	20	85	92
4	66	5	49	88

All reactions conducted in anhydrous benzene, using two equivalents of allyltri-*n*-butyltin

TABLE 8

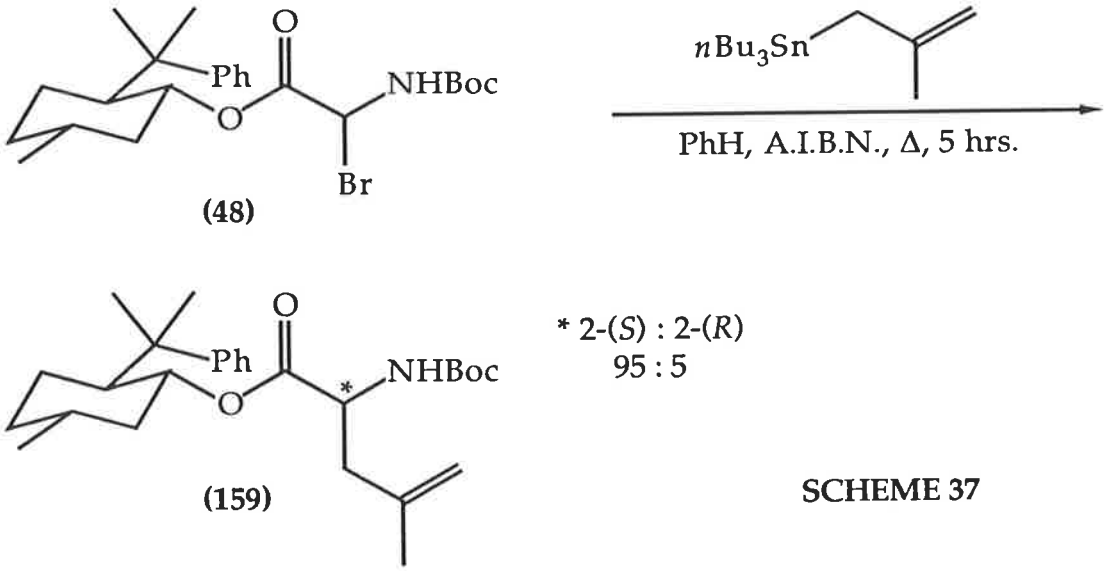
The diastereoselectivity of the allyl transfer reaction did improve, however, when the reaction was carried out at lower temperature. At the same concentration as the initial allylation reaction (66 mM), but at ambient temprature (*ca* 20°C) the 2-(*S*) : 2-(*R*) diastereomer ratio improved to 96 : 4 (Entry 3). Thus, it can be seen that the diastereoselectivity of the allylation reaction exhibits a temperature dependence similar to that of the deuteration reaction, in so far as lowering the reaction temperature increases the 2-(*S*) : 2-(*R*) diastereomer ratio. The extent of this increase, however, is much greater in the case of the deuteration reaction. This is shown by the 42% increase in d.e. which resulted upon decreasing the deuteration reaction temperature from 80°C to 20°C.

The improved yield of 85% obtained in the room temperature allylation of the bromide (**48**) is attributable to a lesser degree of decomposition of the bromide under the milder reaction conditions. This was indicated by the small amount of low R_f material detected by T.L.C. analysis of the crude reaction mixture. The yield observed here is significantly higher than the

yields quoted by Easton and Scharfbillig[98] (63%) and Baldwin *et al*[99] (65%) for allyl transfer to methyl *N*-benzoyl-2-bromoglycinate (**142**)).

An attempt was made to further improve the diastereoselectivity of allyl transfer to the bromide (**48**) by performing the reaction at still lower temperature. A mixture of the bromide, two equivalents of allyl tri-*n*-butyltin and a catalytic amount of A.I.B.N., in benzene solution, was left to stand at 5°C (**Table 7,** Entry 4). The progress of the reaction, as monitored by T.L.C., was extremely slow at this temperature. After sixteen days at 5°C, despite regular addition of fresh A.I.B.N., the yield of allylated product was only 49% after chromatography. This low yield is a result of the very low rate of reaction at 5°C. H.P.L.C. analysis of this product established the 2-(*S*) : 2-(*R*) diastereomer ratio as 94 : 6. This is lower than the 96 : 4 ratio observed for the room temperature reaction. This result is anomolous in light of the marked improvement observed in the diastereoselectivity of this reaction upon lowering the reaction temperature from 80°C to 20°C. However, since the low chemical yield made this low temperature reaction synthetically unattractive, the reproducibility of this result was not investigated.

3.2 β-METHALLYL TRANSFER TO THE BROMIDE (48)



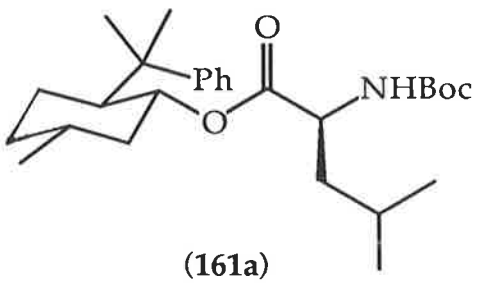
SCHEME 37

Next, the reaction of the bromide (**48**) with β-methallyl tri-*n* butylstannane was studied (**Scheme 37**). Two equivalents of this stannane were added to a solution of the bromide in benzene, in the presence of a catalytic amount of A.I.B.N. The resultant solution was left to stand at room temperature for sixteen hours. Chromatographic purification gave a mixture of the 2-(*S*) and 2-(*R*) β-methallyl substituted products (**159a**) and (**159b**) in a combined yield of 81%. H.P.L.C. analysis of this mixture revealed two peaks in a 95 : 5 ratio with the major component being of lower retention time. This indicated that the major diastereomer formed, as expected, possessed the 2-(*S*) stereochemistry.

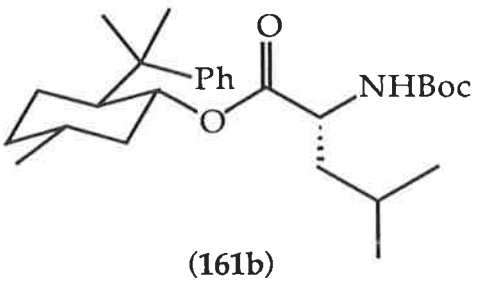
The proton N.M.R. spectrum of the mixture was consistent with the structure of the expected compound. Besides the familiar signals due to the 8-phenylmenthyl groups, signals characteristic of the novel amino acid moiety were observed. The singlet at 1.64 p.p.m. integrating for three protons was attributed to the allylic methyl protons of the unsaturated side chain. Two broadened singlets at δ 4.63 and 4.75 due to the two vinylic

protons were also present. The α-proton signal appeared as a six line pattern centered at δ 3.77. The pattern observed appears to arise from the overlapping of two broadened triplets, with the triplet coupling being 5.6 Hz and the doublet coupling 8.4 Hz. The vicinal amide proton resonated at δ 4.41 as a doublet, with a coupling constant of 8.3 Hz. Therefore, the two overlapping triplets can arise only if the α-proton coupling to one of the diastereotopic β protons is of magnitude 5.6 Hz and coupling to the other β–proton is close to 8.3 Hz. This is indeed the case. Although only the downfield half of the expected ABX pattern due to the allylic, β-methylene protons was completely unobscured (the upfield half being partially obscured by the methylene envelope), both α-β proton couplings were apparent. The AX and BX couplings were found to be 5.3 Hz and 8.4 Hz, accounting for the pattern observed for the α-proton signal.

^{13}C N.M.R. analysis of the mixture detected only one diastereomer. As with the proton N.M.R., the familiar 8-phenylmenthyl signals were accompanied by signals diagnostic for the amino acid moiety. The allylic methyl carbon resonated at δ 21.84, whilst the allylic methylene carbon resonated at δ 40.44. The unsubstituted vinylic carbon resonated at δ 113.89, and the quaternary vinylic carbon at δ 140.95. The α-carbon gave a signal at δ 51.68.



(161a)



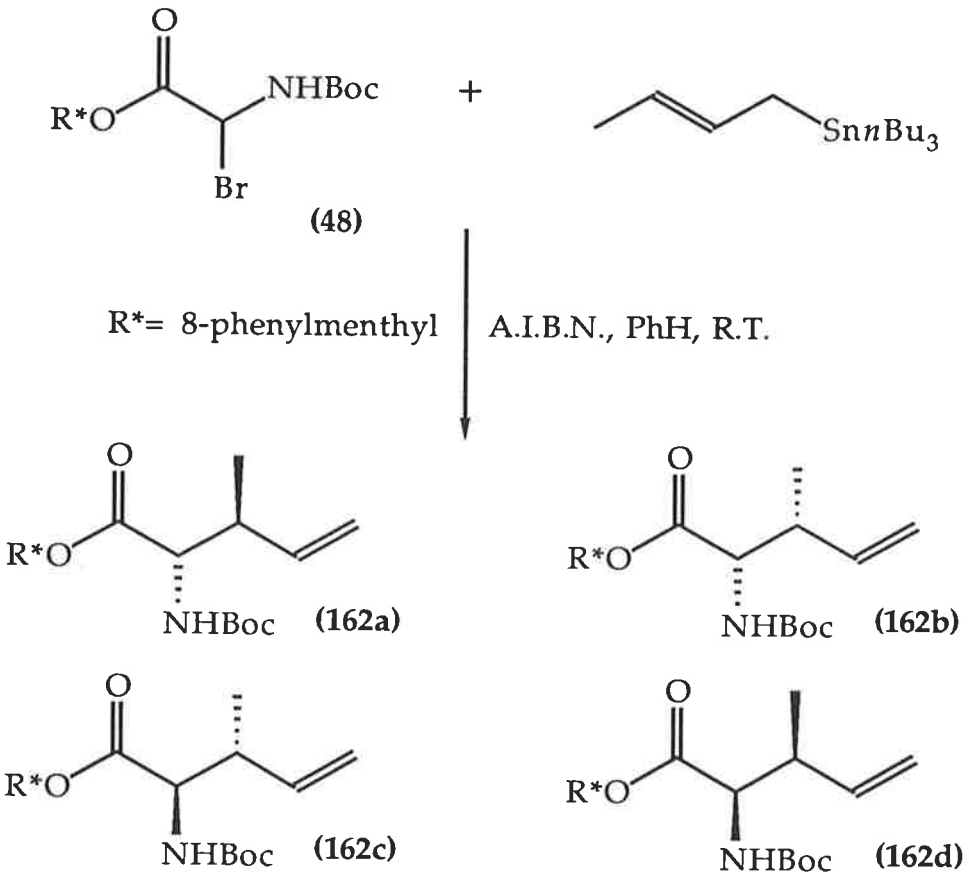
(161b)

FIGURE 39

Although the minor diastereomer (**159b**) was not isolated and characterized, its presence was established by hydrogenation of the 95 : 5 mixture of diastereomers to the leucine derivatives (**160a**) and (**160b**) under standard conditions. H.P.L.C. analysis of these saturated products revealed two components in a 94 : 6 ratio, again with the major component having a lower retention time. The retention times of these compounds differed from those of the two corresponding unsaturated compounds, but correllated with those of the authentic 2-(*S*) 8-phenylmenthyl *N*-*t*-Boc-leucinates (**161a**) and (**161b**) (**Figure 39**). These standards were obtained by preparative H.P.L.C. separation of the fully characterized diastereomeric pair obtained through the coupling of *N*-*t*-Boc-(*R*,*S*)-leucine and 8-phenylmenthol.

The first eluting of the two diastereomers was confirmed as the 2-(*S*) isomer by H.P.L.C. and ^{1}H-N.M.R. correlation with 8-phenylmenthyl *N*-*t*-Boc-(*S*)-leucinate (**161a**), synthesized from (*S*)-leucine. The ^{1}H-N.M.R. spectrum of the hydrogenation product was identical to that of the authentic 2-(*S*) leucinate (**161a**). Thus the major γ-δ-dehydroleucine derivative (**159a**), formed by β-methallyl transfer to the bromide (**48**), possesses the 2-(*S*) stereochemistry. The stereochemical outcome of this reaction is therfore consistent with the model previously described for the analogous reaction with allyl tri-*n*-butyltin, as expected.

3.3 TRANSFER OF A PROCHIRAL ALLYL GROUP TO THE BROMIDE (48)



SCHEME 38

The reaction of 8-phenylmenthyl *N*-Boc-2-bromoglycinate (**48**) with (*E*)-(tri-*n*-butylstannyl)-2-butene represents an important extension of the methodology just developed. As shown in **Scheme 38**, the reaction between the α-centred radical (**120**) and the methyl substituted allylstannane involves the coupling of two prochiral centres, namely the *sinister* diastereoface of the radical and an enantioface of the olefin. This reaction, therefore, has the potential to give rise to the four diastereomers shown in **Scheme 38**. The highly diastereoselective reaction of the bromide with allyl and β-methallyl tri-*n*-butylstannanes demonstrated the

ability of this system to control the absolute stereochemistry of the α-centre. Therefore, it was expected that the two 2-(*R*) products (**162c**) and (**162d**) would be formed in only minor amounts. Hence, only the question of stereoselectivity at the β−centre (i.e., the (2*S*,3*S*) : (2*S*, 3*R*) ratio) remained.

Clearly, for high asymmetric induction to be achieved at the β-centre of the resultant γ-δ-unsaturated α-amino acid derivative (**162**) , one of the enantiotopic faces of the 2-butenyl moiety of the stannane must preferentially approach the α-centred radical. The absolute configuration of the resultant β-centre is dependent on which particular face of the prochiral stannane is prefered.

Accordingly, the bromide (**48**) was treated with (*E*)-γ-methallyl tri-*n*-butylstannane under the optimum conditions already established (two equivalents of stannane and a catalytic amount of A.I.B.N. in benzene at room temperature for sixteen hours). The crude material was subjected to chromatographic purifiction in order to remove tin residues and low R_f material. H.P.L.C. analysis of the purified product (obtained in 83% yield) revealed one high intensity peak accompanied by four very minor, lower retention time peaks and a higher retention time tail. As previously shown, the C-2 epimers of these *N*-*t*-Boc-α-amino acid 8-phenylmenthyl esters are quite well resolved by H.P.L.C. Therefore it appeared that, since no other peaks of significant intensity were observed, the stereoselectivity at C-2 was very high for this reaction. However, the amount of selectivity at C-3 was impossible to gauge by H.P.L.C, as it was unknown whether the (2*S*, 3*S*) and (2*S*, 3*R*) diastereomers coeluted or not.

Proton and carbon N.M.R. were then utilized in an effort to determine the amount of induction at the β-centre. The proton N.M.R. spectrum of the olefin (**162**) contained only one tertiarybutyl methyl resonance and only two 8-phenylmenthyl geminal dimethyl resonances. It appeared that a pair of doublets, integrating for three protons in total, due to the β-methyl group of (**162**), were present. This suggested a mixture of diastereomers. However, these signals were obscured by the doublet due to the ring methyl group of the 8-phenylmenthyl moiety and could not be relied upon to assess optical purity.

It was expected that the α proton of each diastereomer would appear as a doublet of doublets in the ^{1}H-N.M.R. spectrum due to coupling with both an amide and β-proton. Two overlapping doublets of doublets were indeed present in the spectrum and were assigned to the α-protons of the two diastereomers. The major doublet of doublets was centred at δ 3.58 p.p.m., with coupling constants of 4.2 Hz and 8.6 Hz. The minor doublet of doublets was centred at δ 3.63, with coupling constants of 4.0 Hz and 8.7 Hz. Due to the overlap of the two patterns, it was impossible to determine the diastereomer ratio by integration of these signals. However, if decoupling at the resonant frequency of the nucleus responsible for the larger coupling in this system (the amide proton) was possible, two integrable doublets would result. A broadened doublet centred at δ 4.92 p.p.m. with J=8.8 Hz was assigned as an amide proton. Decoupling at this frequency resulted in the major, low field doublet of doublets collapsing to a doublet, with J=4.0 Hz. However, the minor doublet of doublets was unaffected and overlapped with the new doublet, frustrating attempts at integration of the two signals. It was thus apparent that the amide proton chemical shift of the minor diastereomer differed from that of the major diastereomer. However, the complexity of this

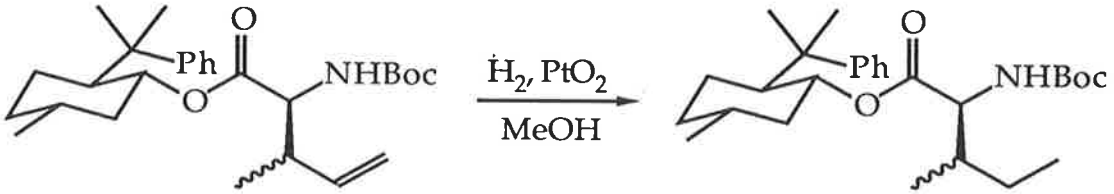
region of the spectrum prevented the assignment of any signal to the amide proton of the minor diastereomer.

The chromatographic homogeneity of this compound, along with the fact that α-epimers in this series generally have a much larger α-proton chemical shift difference, suggested that these two diastereomers were epimeric at the β-carbon rather than the α-carbon. The ^{13}C-N.M.R. spectrum of this compound was consistent with this supposition. Most of the carbon atoms of the 8-phenylmenthyl moiety diplayed one resonance each. Exceptions were the ring methyl carbon (28.49, 28.38 p.p.m.), C-2' (41.53, 41.48 p.p.m.), one of the geminal methyl carbons (24.38, 24.25 p.p.m.) and the alkoxy ester carbon C-1' (75.79, 75.71 p.p.m.). The small chemical shift difference (0.08 p.p.m.) between the two C-1' signals contrasted sharply with the large difference (0.9 p.p.m. on average) between the C-1' signals of α-epimers in this series.

Within the amino acid moiety, only one tertiarybutyl resonance was observed. However, the α-carbon (57.12, 56.90 p.p.m.), β-carbon (40.25, 39.67 p.p.m.), γ-carbon (15.72, 14.90 p.p.m.), vinyl methylene (116.16, 115.40 p.p.m.) and vinyl methine (138.80, 137.85 p.p.m.) carbons all gave two signals. As the ratio of intensities for these paired signals ranged from 3:2 to 9:2, ^{13}C-N.M.R. could not be reliably used to measure the (2*S*,3*S*) : (2*S*,3*R*) diastereomer ratio.

It was apparent that a more concise and unambiguous determination of the diastereomer ratio and the C-2, C-3 stereochemistry of each diastereomer was needed. Inspection of the carbon skeleton of the α-amino acid moiety of the unsaturated product (**162**) revealed an obvious relationship to the carbon skeleton of the naturally occurring α-amino

acid isoleucine. Simple catalytic hydrogenation of the double bond of (**162**) would yield the isoleucine derivative (**163**) (**Scheme 39**). Correlation with the relevant authentic *N*-*t*-Boc-isoleucine 8-phenylmenthyl esters would then unequivocally establish the amount of asymmetric induction at the α and β-centres for the allyl transfer reaction of bromide (**48**) with (Z)-(tri-*n*-butylstannyl)-2-butene.



(**162**) (**163**)

SCHEME 39

As both the α and β-carbon atoms of isoleucine are chiral, four diastereomeric isoleucines exist (as two pairs of enantiomers). Synthesis of the *N*-*t*-Boc derivative of a commercially available equimolar mixture of the four stereoisomers, followed by esterification with 8-phenylmenthol, yielded an equimolar mixture of the four compounds (**117a**), (**117b**),(**117c**), (**117d**), whose structures are shown in **Scheme 22**, Chapter 1, Results and Discussion 1.6.

Of course, due to the presence of the covalently bound homochiral auxiliary, no enantiomeric relationships exist between any of the four stereoisomers. Hence it was expected that simple achiral H.P.L.C. analysis would enable resolution of all four stereoisomers. In practice, however, three peaks in a roughly 2:1:1 ratio were detected in the H.P.L.C. chromatogram of the mixture. This indicated that two of the four diastereomers coeluted.

In order to establish which particular diastereomer was represented by each peak, all four diastereomeric isoleucines were purchased and each converted to its *N*-*t*-Boc/8-phenylmenthyl ester derivative under standard conditions. The (2*S*, 3*S*)and (2*S*, 3*R*) compounds (**117a**) and (**117b**) were subsequently found to possess the same retention time by H.P.L.C. This retention time was coincident with that of the lowest retention time peak (double the area of the other two peaks) in the H.P.L.C. chromatogram of the mixture. The next highest retention time peak was that of the (2*R*, 3*S*) diastereomer (**117d**). The last eluting diastereomer (**117c**) possessed the (2*R*, 3*R*) stereochemistry.

The ^{1}H-N.M.R. spectra of the four diastereomeric isoleucine derivatives (**117a**), (**117b**), (**117c**) and (**117d**) all contained the expected signals due to the 8-phenylmenthyl and tertiarybutyl groups. In addition, the isobutyl methyl groups gave distinct characteristic signals in some cases. The spectrum of the (2*S*,3*S*)-isoleucinate (**117a**) contained a doublet signal (J=6.8 Hz), centred at δ 0.76, due to the γ-methyl protons and a triplet signal (J=7.4 Hz) due to the δ-methyl protons. The spectrum of the (2*S*,3*R*)-isoleucinate (**117b**) contained a doublet (J=6.9 Hz) centred at the very low chemical shift of δ 0.66 due to the γ-methyl protons. The δ-methyl triplet overlapped with the ring methyl doublet. The (2*R*,3*S*)-isoleucinate (**117c**) gave a doublet signal (J=6.8 Hz) at δ 0.78 due to the γ-methyl protons and a triplet signal centred at δ 0.91 (J=7.4 Hz) due to the δ-methyl protons. Both the γ and δ-methyl signals of the (2*R*,3*R*) diastereomer (**117d**) were indistinguishable due to overlap with each other and with the ring methyl doublet.

Most significantly, however, the α-proton of each diastereomer resonated as a doublet of doublets at distinctly different chemical shifts. **Table 9**

summarizes the relevant data. This meant that integration of the α-proton signals of the product derived from hydrogenation of the olefin (**177**) would yield the (2*S*, 3*S*) : (2*S*, 3*R*) ratio, and hence, the amount of induction at the β-centre.

ENTRY	No.	C-2, C-3 CONFIGURATION	$\delta_{\alpha\text{-H}}$	$J_{2\text{-HN}}$ (Hz)	$J_{2\text{-3}}$ (Hz)
1	(**117a**)	(2*S*, 3*S*)	3.53	8.2	3.7
2	(**117b**)	(2*S*, 3*R*)	3.66	8.9	3.3
3	(**117c**)	(2*R*, 3*R*)	4.13	9.3	4.8
4	(**117d**)	(2*R*, 3*S*)	4.26	8.2	3.7

TABLE 8

Accordingly, a methanolic solution of the γ-δ-dehydroisoleucine derivative (**162**) was treated with 5% palladium on carbon under one atmosphere of hydrogen. ^{1}H-N.M.R. analysis of the product, however, revealed that no detectable hydrogenation had occurred. After several unsuccessful attempts at hydrogenation with the same catalyst, use of platinum oxide met with immediate success. Shown in **Figure 40** is the α-proton region of the ^{1}H-N.M.R. spectrum of the hydrogenation product (**163**). The chemical shift of the two doublets of doublets present correspond with those of the (2*S*, 3*S*) and (2*S*, 3*R*) isoleucine derivatives (**117a**) and (**117b**), as indicated. Integration of the two multiplets yields a (2*S*,3*S*) : (2*S*,3*R*) ratio of *ca.* 2 : 3, indicating a slight *threo* selectivity for the allyl transfer reaction.

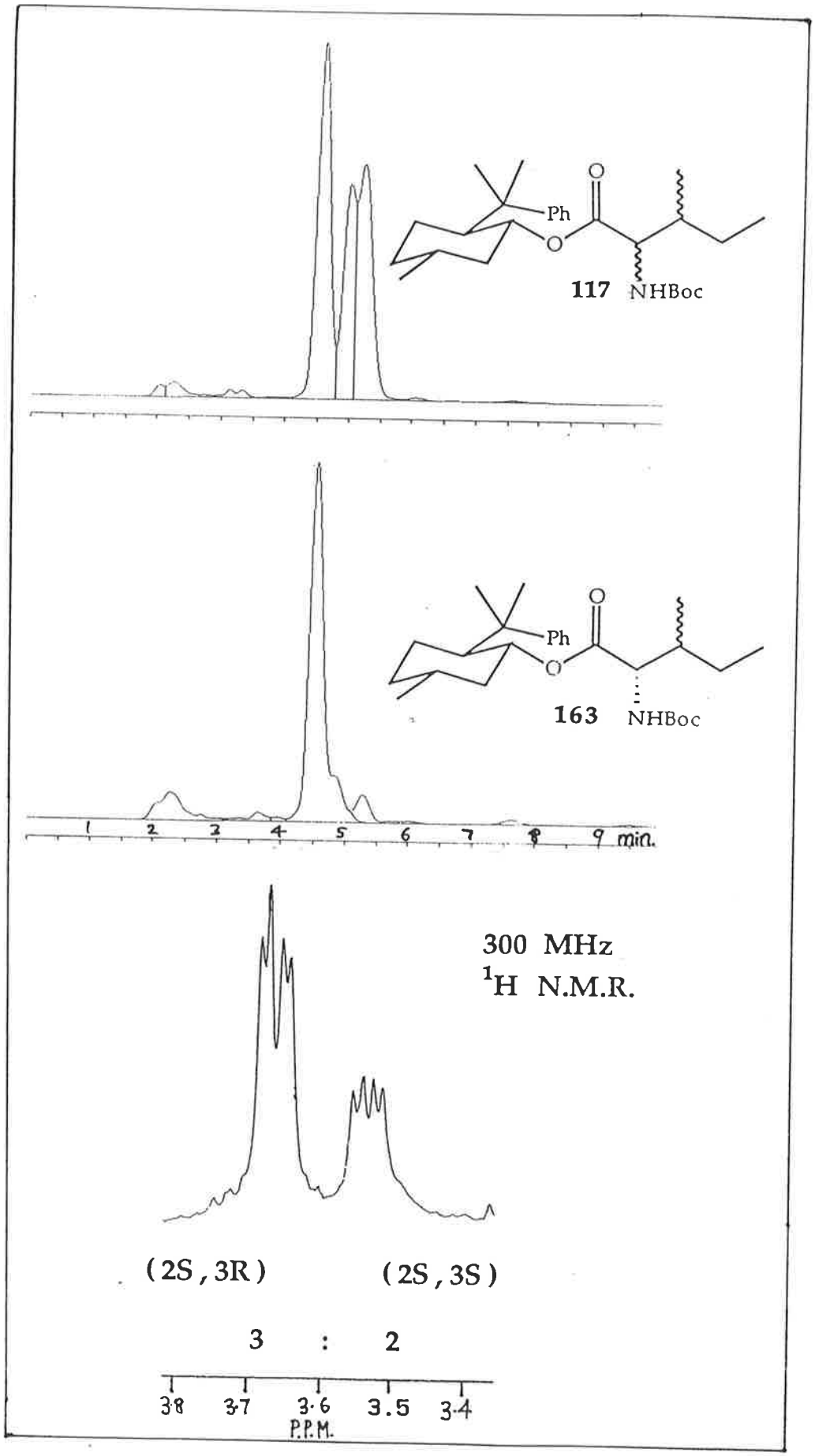

Ph
O
O
117 NHBoc
Ph
O
O
163 NHBoc
1 2 3 4 5 6 7 8 9 min.
300 MHz
^{1}H N.M.R.
(2S, 3R)
(2S, 3S)
3 : 2
3·8 3·7 3·6 3.5 3·4
P.P.M.

FIGURE 40

The H.P.L.C. chromatogram of the reduction product (shown in **Figure 40**) revealed a small peak attributed to unreduced material and another attributed to the (2*R*, 3*R*) diastereomer. It was impossible to detect any of the (2*R*, 3*S*) diastereomer as the retention time which it was expected was obscured. Hence, the total (2*S*) : (2*R*) ratio can only be estimated as 93:7.

3.4 HYDROLYSIS OF 8-PHENYLMENTHYL *N-t*-BOC-(*S*)-ALLYLGLYCINATE (172a)

The hydrolysis of 8-phenylmenthyl *N-t*-Boc-(*S*)-allylglycinate (**157a**) to give enantiomerically pure (*S*)-allylglycine (**164**) was investigated next. A sample of the diastereomerically pure 2-(*S*)-allylglycinate (**157a**) was obtained by chromatographic purification of a 96:4 2-(*S*) : 2-(*R*) mixture derived from the asymmetric allyl transfer reaction. The purity of this chromatographed sample was established to be >99% by H.P.L.C. analysis, which failed to detect the minor, 2-(*R*)-allylglycinate (**157b**).

Following the previously established procedure, the ester was treated with trifluoroacetic acid for fifteen minutes, whereupon a twofold volume of 6N HCl was added. Reflux of this mixture for sixteen hours, followed by ion exchange chromatography of the crude, water-soluble hydrolysate gave a product in 65% yield (assuming that it had the molecular weight of allylglycine). This product was then analyzed by polarimetry. Its specific rotation was $[\alpha]_D^{24} = -30.3^\circ$ (C=3.77, H_2O). Based on the reported[103] specific rotation of $[\alpha]_D^{24} = -37.1^\circ$ (C=4, H_2O), it appeared that the allyglycine obtained was not enantiomerically pure. However, as previously stated, optical rotation measurements are subject to many factors which render them somewhat unreliable, especially when charged molecules like amino acids are involved. Therefore other criterea of optical purity were sought.

The low rotation of this sample was not necessarily due to low enantiomeric purity of the allylglycine produced, but may have been due to the presence of other impurities. Hence, the ^{1}H-N.M.R. of the hydrolysis product was compared to that of authentic (*R*, *S*)-allylglycine.

The two spectra were identical in every respect save for the presence of a doublet resonance at δ 1.11 p.p.m. in the spectrum of the hydrolysate. Assuming that this signal is due to a methyl group, its integral, relative to those of the allylglycine signals, indicates that the impurity is *ca* 17 mole % of the mixture. Obscure peaks in the N.M.R. spectrum may have been due to the same impurity. It is highly probable that this impurity is responsible for the specific rotation of the allylglycine being *ca* 18% lower than that reported for enantiomerically pure allyglycine. The identity of the compound giving rise to the extraneous methyl doublet may well be 4-hydroxynorvaline, the product expected due to Markovnikov hydration of the double bond under the acidic hydrolysis conditions. An ion of m/z 134 (the molecular weight of protonated 4-hydroxynorvaline), present in the mass spectrum of the purified hydrolysate sample, supports this speculation. The intensity of this peak was 18% of the intensity of the peak of m/z 118 (protonated allylglycine). This correlates with the estimation of 17% made for the impurity revealed by the ^{1}H-N.M.R. spectrum of this mixture.

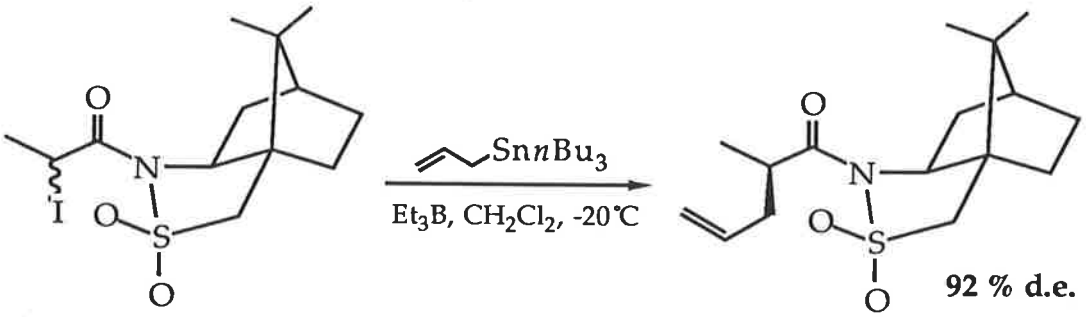
It was apparent that a more reliable means of determining the optical purity of the allylglycine derived from hydrolysis of (**157a**) was needed. Conversion of the amino acid back to its *N*-*t*-Boc/8-phenylmenthyl ester derivative (**157a**) was considered to be the most expedient method, since H.P.L.C. conditions for the resolution of the 2-(*S*) and 2-(*R*) 8-phenylmenthyl *N*-*t*-Boc-allylglycinates were already established.

Conversion to the *N*-*t*-Boc derivative was straightforward. Because this compound potentially contained two enantiomeric acids, esterification of this derivative with 8-phenylmenthol was carried out using a 5% excess of the alcohol in order to avoid kinetic resolution of the enantiomers.

H.P.L.C. analysis of the esterification product revealed the presence of 8-phenylmenthyl *N*-*t*-Boc-(*S*)-allylglycinate (**79a**) along with 1.5-1.8% of the corresponding (*R*)-allylglycinate (**79b**). This indicated that a maximum of 1.8% racemization of the allyglycine had occurred during hydrolysis.

Thus, although the hydrolysis procedure produced a chemically impure sample of allylglycine, the allylglycine itself was of high optical purity. Purification of the allylglycine by recrystallization would provide a sample of both high chemical and optical purity. As restraints in time and the amount of material available existed, purification of the amino acid was not attempted.

3.5 DIASTEREOSELECTIVE ALLYL TRANSFER TO ACYCLIC RADICALS : LITERATURE REPORTS



(165) SCHEME 40 (166)

During the latter stages of this work, some reports on asymmetric homolytic carbon-carbon bond formation involving prochiral, acyclic radicals appeared in the literature. D.P. Curran's group at Pittsburgh showed that the chiral α–iodoamide (**165**) underwent highly diastereoselective allylation with allyltri-*n*-butyltin[104] (**Scheme 40**). The authors argued that the amide oxygen and sultam O^1 are opposed due to dipole repulsion, and that the amide radical has *Z* geometry as the *E* substituent is quite close to the sultam O^1 (see **Figure 41**). Hence, approach to the *rectus* (top) face of the planar system is favoured as the stannane would experience a significant 1,4-interaction with the sultam O^2 when approaching from the *sinister* (bottom) face.

The principles established by Guindon *et al.* in their work on the diastereoselective tri-*n*-butyltin hydride reduction of a prochiral, acyclic radical (discussed in Chapter 2) were extended by this group to asymmetric, radical, carbon-carbon bond formation through homolytic allyl transfer[105]. The secondary iodide (**167**), when treated with allyltri-*n*-butyltin at low

A.I.B.N.
temperature using ~~triethylboron~~ as a radical initiator, gave the allylated product (**168**) with 89% d.e. (**Scheme 41**).

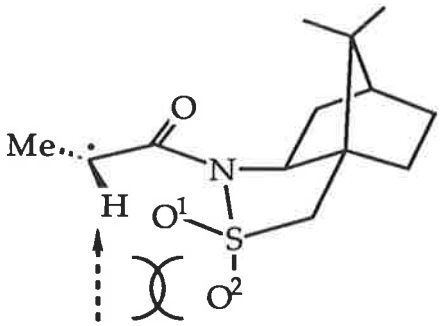
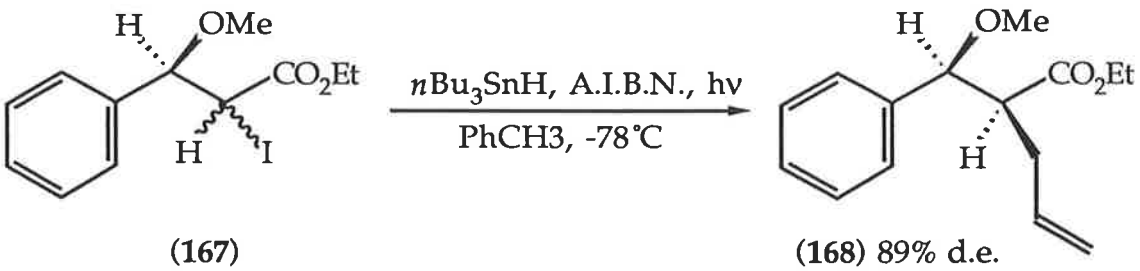


FIGURE 41



(**167**) (**168**) 89% d.e.

SCHEME 41

3.6 ALLENYL AND PROPARGYL TRANSFER TO THE BROMIDE (48)

The synthesis of the α-allenylglycine derivative (**169**) (**Figure 42**) *via* the reaction of the bromide (**48**) with propargyltriphenyl stannane (**150**) was next attempted. The stannane was produced by use of the method of Le Quan and Cadiot[106], which involved treatment of propargylmagnesium bromide with chlorotriphenyl stannane. This procedure also gave a small amount of allenyl triphenylstannane (**170**). The two products were readily distinguishable by their infrared spectra and melting points, and separable by fractional crystallization from hexane.

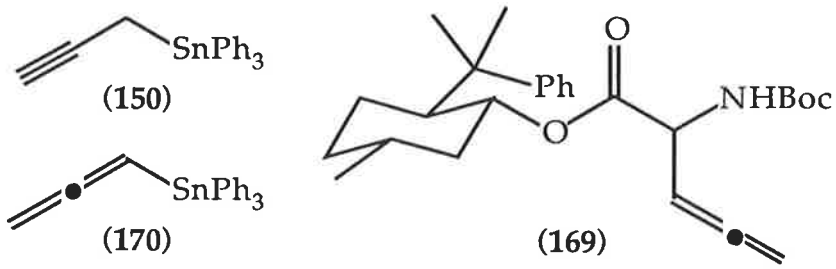


FIGURE 42

The 2-bromoglycinate (**48**) was treated with two equivalents of propargyltriphenylstannane and a catalytic amount of A.I.B.N. in refluxing benzene for five hours. Chromatographic removal of tin compounds and low R_f material gave a mixture of products in a combined yield of 45%. ^{1}H-N.M.R. analysis of the mixture revealed only one tertiarybutyl methyl resonance, but two pairs of geminal methyl singlets and two ring methyl doublets were detected. The ratio of the two products was approximately 2 : 1. The fact that only one tertiarybutyl resonance was detected strongly suggested that the two compounds were not simply C-2 epimers, since precedence had established that a 0.2-0.3 p.p.m. difference between resonances would have been observed if this were the case.

FIGURE 43

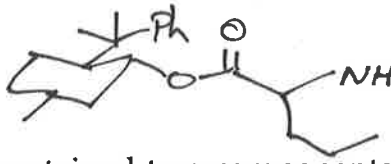
Baldwin *et al*[107] had reported that, in the presence of A.I.B.N., thermolysis of propargyltriphenyl stannane (**150**) resulted in partial isomerization to allenyltriphenyl stannane (**170**) *via* the competing S_H2' reaction of triphenylstannyl radical with the acetylene (**Figure 43**). Although Baldwin stated that allenyltriphenyl stannane was unreactive under homolytic conditions, it was considered that one of the products in this mixture could have arisen from the reaction of this stannane with the bromide, perhaps through an alternative mechanism.

It was thus necessary to determine what, if any, product resulted from treatment of the bromide with allenyltriphenyl stannane and a catalytic amount of A.I.B.N. in refluxing benzene. ^{1}H-N.M.R. analysis of the product of this reaction (obtained in 53% yield) detected predominantly one compound. The spectrum obtained matched that of the minor compound produced in the previous reaction. In addition, a small peak 0.03 p.p.m. upfield of the tertiarybutyl methyl resonance was present, suggestive of a minor, C-2 epimer. The spectrum displayed all of the usual features of the α-substituted 8-phenylmenthyl *N*-*t*-Boc-glycinates in this series. In addition, the α-proton resonated as a complex multiplet at δ 4.09 and complex signals integrating for three protons appeared at δ 4.90-5.15 (i.e., in the vinylic region).

The I.R. spectrum of this compound contained a peak at $\bar{\nu}$ 1958 cm^{-1}, indicating the presence of an allenyl group. No peaks assignable to a

terminal alkyne were present. This suggested that the α-allenylglycine derivative (**169**) was the product of this reaction.

The ^{13}C-N.M.R. spectrum of this compound was also consistent with the proposed structure. The α-carbon resonance at δ 51.53 was accompanied by signals at δ 79.43 and δ 89.06 (CH_2 and CH respectively). The chemical shifts of the latter two signals are too low for vinylic carbon atoms but are within the range expected for terminal allenic carbons. A low intensity signal at δ 207.19 confirmed the presence of an allenyl group. The mass spectrum of this product revealed a peak due to the molecular ion at m/z 427 and an M-1 peak at m/z 426. This hydride loss is typical of allenes[108].

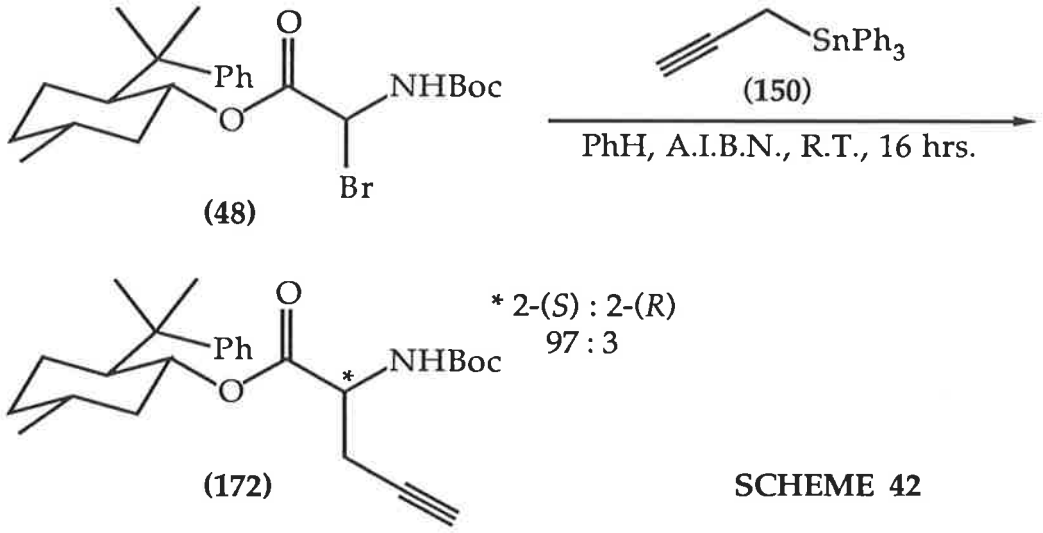


(171)

H.P.L.C. analysis of the product revealed that it contained two components in a 93:7 ratio, with the major component having the lower retention time. Hydrogenation of this mixture yielded (**171**), a 93:7 mixture of two compounds which co-eluted with the two components of genuine 8-phenylmenthyl *N*-*t*-Boc-(*R*,*S*)-norvalinate (**75a**) and (**75b**).

The ^{1}H-N.M.R. spectrum of the hydrogenated product was identical to that of authentic 8-phenylmenthyl *N*-*t*-Boc-(*S*)-norvalinate (**75a**), except for the presence of the tertiarybutyl methyl signal of the (*R*)-norvalinate as a small shoulder 0.03 p.p.m. upfield of the complementary signal of the major diastereomer. This observation, along with the fact that the major hydrogenation product co-eluted with the authentic 2-(*S*)-norvalinate (**75a**), establishes that the C-2 conformation of the predominant allenic diastereomer is also (*S*).

This work established that the minor product formed upon treatment of the bromide (48) with propargyl triphenylstannane in refluxing benzene was the α-allenyl compound (**169**), and that it arose through reaction of the bromide with allenyltriphenyl stannane (formed by isomerization of propargyltriphenyl stannane). It then remained to establish the identity of the major product formed in this reaction, and its mode of formation.



SCHEME 42

It was suspected that this major product was the propargylglycine derivative (**172**), formed by the reaction of the bromide with propargyltriphenyl stannane. Therefore it was necessary to conduct this reaction under conditions that would not isomerize the propargyl stannane to the allenyl stannane. It was considered that a lower reaction temperature would suppress this isomerization. Accordingly, the 2-bromoglycinate (**48**) was treated with two equivalents of propargyltriphenylstannane (**150**) and a catalytic amount of A.I.B.N. in benzene at room temperature (**Scheme 42**). After sixteen hours, the crude reaction product was purified by chromatography. The infrared spectrum of the purified product contained an absorption at $\tilde{\nu}$ 3300 cm^{-1} due to a terminal acetylenic C-H stretch, and no allenyl stretch at 1958 cm^{-1}.

Curiously, no peak due to the triple bond stretch was present in the infrared spectrum. However, N.M.R. spectral evidence left little doubt that an acetylene group was present in the molecule. The product (**172**) gave a molecular ion of m/z 427, but no M-1 peak was present in the mass spectrum.

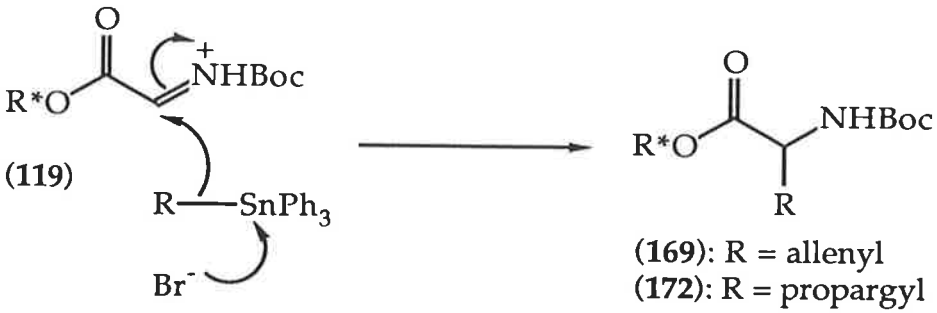
The only compound detected by ^{1}H-N.M.R. spectroscopy had an identical spectrum to that of the major compound formed in the reaction of bromide (**48**) with propargyltriphenylstannane at 80°C. The α-proton of this product resonated as a doublet of triplets centred at δ 3.59. The doublet coupling of 7.8 Hz matched the coupling of the amide proton doublet centred at δ 5.08. The triplet pattern indicated that the α-proton was coupled to two β-methylene protons, as would be expected for an α-propargylglycine derivative. Although these β-protons would necessarily be diastereotopic, it is not unreasonable that both α-β couplings could have similar magnitudes.

The AB portion of this inferred ABX system was centred at δ 2.27 p.p.m., with a geminal AB coupling of 16.9 Hz. Analysis of this system yielded the values J_A = 4.1 Hz and J_{BX} = 4.0 Hz, which were indeed of similar magnitude, though not equal, to the triplet coupling of 4.4 Hz present in the α-proton multiplet. However, decoupling at the α-proton frequency resulted in the collapse of the 4.1 Hz and 4.0 Hz couplings, confirming the connectivity between the protons responsible for these three signals. Each diastereotopic β-proton displayed a further, small coupling (of 2.5 Hz and 2.8 Hz, respectively) to another proton. The magnitude of these couplings suggested that they were long-range. Four-bond coupling to the acetylenic proton of the propargyl unit accounts for this observation. This proton resonated as a broad singlet at δ 2.08.

All of these data were consistent with the presence of a propargyl group at the α position of the glycine moiety. The ^{13}C-N.M.R. spectrum of the product further confirmed this structure. The diagnostic peaks in this spectrum were at δ 70.91 (quaternary C) and δ 79.03 (methine C), due to the acetylenic carbons, and at δ 22.37, due to the β, propargylic carbon.

H.P.L.C. analysis of the product revealed the presence of two components in a 97:3 ratio. Again, the major component of the mixture eluted first. Hydrogenation of the mixture gave a product (**173**) which contained two components, also in a 97:3 ratio. The major component of the hydrogenated mixture coeluted with 8-phenylmenthyl *N*-*t*-Boc-(*S*)-norvalinate (**75a**), whilst the minor component coeluted with the (*R*)-norvalinate (**75b**). The ^{1}H-N.M.R. spectrum of the hydrogenated mixture was identical to that of the authentic (*S*)-norvalinate, except for a signal due to the *t*-Boc methyl protons of the (*R*)-norvalinate, present as a small shoulder upfield of the major *t*-Boc methyl peak.

This work unequivocally shows that, unexpectedly, the bromide (**48**) reacts with propargyltriphenylstannane to give the corresponding α-propargylglycine derivative (**172**), and with allenyltriphenyl stannane to give the α-allenylglycine isomer (**169**). That these products were obtained indicate that, in these reactions, the glycinyl moiety couples with the carbon atom α, and not γ, to the tin. Unlike the classical homolytic allyl transfer mechanism, this coupling would not involve the transposition of π electrons within the carbon unit being transferred. Therefore, the mechanism operating here is not the radical S_H2' mechanism.

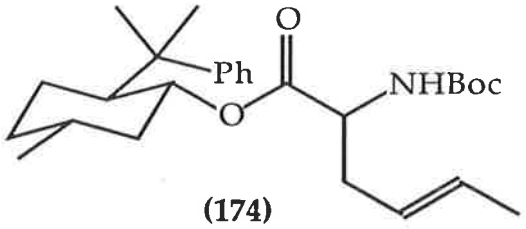


R* = 8-phenylmenthyl

FIGURE 44

A reaction mechanism which does not involve radicals, but rather, invokes ionic intermediates, also accounts for the products obtained. Heterolysis of the carbon-bromine bond gives the iminium species (**119**) and bromide ion. Attack by bromide ion on the halophilic tin atom polarizes the carbon-tin bond, rendering the allenyl and propargyl groups nucleophilic. The allenyl and propargyl "anions" then alkylate the α carbon of the iminium cation, as shown in **Figure 44**.

The fact that phenyl transfer does not occur does not rule out this ionic mechanism, as the phenyl anion is not resonance stabilized. Both the allenyl and propargyl anions are stabilized by delocalization of the negative charge, since the σ orbital which formally contains the charge can overlap with the neighbouring π orbital in both cases. In the case of the phenyl anion, no such overlap is possible since the π system is orthogonal to the σ orbital housing the negative charge. However, this mechanism cannot be operating in the allyl transfer reactions dicussed previously, since the product of coupling α to the tin atom ((**174**), **Figure 45**) in the reaction of the bromide (**48**) with (*E*)-(tri-*n*-Butylstannyl)-2-butene was not detected.



(174)

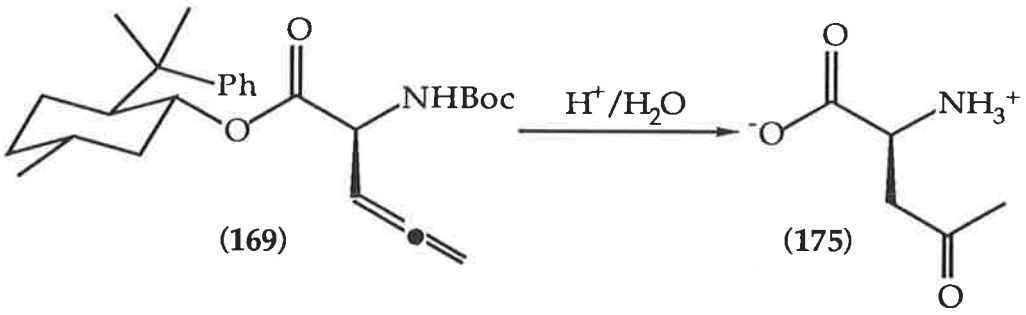
FIGURE 45

3.7 ALLYL TRANSFER IN THE PRESENCE OF A RADICAL INHIBITOR

An attempt was made to eliminate the mechanistic ambiguity that existed due to the products obtained in the reaction of the bromide (**48**) with allenyl and propargyl triphenylstannanes. The results of these experiments cast doubt on whether the alkyl transfer reactions of the bromide were indeed radical in nature. Consequently, the reaction of the bromide with allyltri-*n*-butylstannane was carried out in the absence of A.I.B.N., but in the presence of the radical inhibitor, hydroquinone, and in the dark. The quantity of radical inhibitor used was ten mole % relative to the amount of allytributylstannane. Under these conditions, T.L.C. analysis indicated that allyl transfer to give mainly the 2-(*S*) allyglycinate (**157a**) proceeded at the same previously observed rate. H.P.L.C. analysis of the mixture also revealed that the 2-(*S*):2-(*R*) ratio was 96:4, the same ratio obtained when the reaction was conducted in the presence of A.I.B.N. and with no measures taken to preclude light.

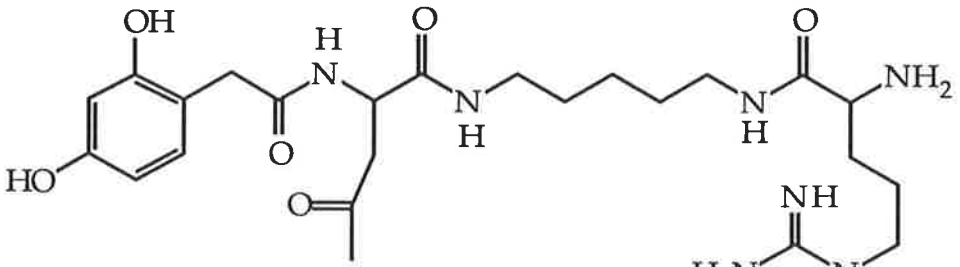
This result does not necessarily indicate that the allyl transfer reaction is not a radical reaction. Radical reactions may still proceed in the presence of radical inhibitors if the radicalophile employed (in this case, allyltri-*n*-butyltin) is a more efficient radical scavenger than the radical inhibitor. In short, the result of this experiment was inconclusive.

Irrespective of the finer details of the mechanism involved, this process yields amino acid derivatives of extremely high optical purity. Although acid-catalyzed hydrolysis of the propargylglycine derivative was not attempted, if successful, propargyl glycine, an inhibitor of the pyridoxal dependent enzyme γ-cystathionase[109,110], would be produced.



SCHEME 43

Acid-catalyzed hydrolysis of the allenyl glycine derivative (**169**) would almost certainly (in light of the partial double bond hydration during hydrolysis of (**157a**)) give rise to 2-amino-4-oxo-pentanoic acid (**175**) through hydration of the allenyl group (**Scheme 43**). The hydration of an α-allenyl α-amino acid derivative to (**175**) under attempted acid-catalyzed hydrolysis has been reported by Castelhano[37]. This amino acid is of interest in its own right as it is a component of argiotoxin-636 (**176**), (**Figure 46**), found in some spider venoms[111]. This compound is under investigation as a treatment for stroke victims[111].



Argiotoxin - 636 (**176**)

FIGURE 46

EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada.

Infrared Spectra were recorded as films on a Jasco A-102 Spectrophotometer using the 1603 cm^{-1} band of polystyrene as a reference.

60 MHz ^{1}H-N.M.R. spectra were recorded on either a Jeol JNM-PMX spectrometer or a Varian T60 spectrometer. 300 MHz ^{1}H-N.M.R. spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. ^{13}C-N.M.R. spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer. Unless otherwise stated, chemical shifts have been quoted in parts per million (p.p.m.) downfield from tetramethylsilane. Peak multiplicities have been abbreviated to s (singlet); d (doublet); t (triplet) and q (quartet).

All thin layer chromatography was performed on Merck DC-Alufolien Kiselgel 60 F_{254} Art. 5554. T.L.C. plates were developed using a solution of 10% w/v ammonium molybdate in 1M HCl followed by heating. Flash Chromatography[67] was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Dry column chromatography[66] was performed on Merck Kieselgel 60 HF_{254} Art. 7739.

H.P.L.C. chromatography was carried out using a Waters 6000A solvent pump and a Waters Model 441 Absorbance Detector operating at 254 nm, in conjunction with an I.C.I. D.P-700 data station. A Waters Radial Pak normal phase 10 μm silica column (8 mm) was used.

Electron impact mass spectra were recorded with an AEI MS-30 double focussing mass spectrometer operating at 70 eV. F.A.B. mass spectra were recorded with a Vacuum Generators ZAB 2HF mass spectrometer with argon gas and a glycerol matrix.

All solvents were distilled before use. Anhydrous diethyl ether, tetrahydrofuran and benzene were obtained by distillation from benzophenone ketyl.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexanol

((–)-8-phenylmenthol) (45)

Followed the method of Ort[56]. The title compound was obtained in 39% overall yield from (*R*)-(+)-pulegone (Aldrich 85%). $[\alpha]_D^{20} = -26.4° \pm 0.5°$. Lit.[56] : $[\alpha]_D^{20} = -26.4° \pm 0.1°$. ^{1}H-N.M.R. (300 MHz) δ: 0.88 d, *J* 6.7 Hz, 3H (ring CH_3); 1.29, s, 3H (CH_3CPh); 1.42, s, 3H (CH_3CPh); 0.75-1.90 complex, 9H; 3.52, d of t, *J* 4.3, 10.2 Hz, 1H (HC-OH); 7.10-7.45, m, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.96 (CH_3CPh); 24.20 (CH_3CPh); 26.39 (ring CH_2CHCPh); 28.63 (ring CH_3); 31.43 (ring $CHCH_3$); 34.80 (ring CH_2CHCH_3); 39.70, (CMe_2Ph); 45.26 (ring CH_2C-O); 54.06 (ring CHCPh); 72.87 (H-C-O); 125.71, 128.37, 151.26, (Ar). ν_{max} 3410 and 3560 cm^{-1}.

SYNTHESIS OF *N*-TERTIARYBUTOXYCARBONYL AMINO ACIDS:

The following *N*-tertiarybutoxycarbonyl amino acids were synthesized from the corresponding amino acids by the method of Itoh, Hagiwara and Kamiya [38]. All are known compounds. In the cases where the compounds were obtained as solids, their melting points corresponded to the reported values. In the cases where the compounds were obtained as oils, ^{1}H-N.M.R. analysis gave spectra which were consistent with the compound structure.

N-*tertiarybutoxycarbonyl*-(R,S)-*alanine (67)*

N-*tertiarybutoxycarbonyl*-(S)-*alanine (67a)*

N-*tertiarybutoxycarbonyl*-(R,S)-*norvaline (68)*

N-*tertiarybutoxycarbonyl*-(S)-*norvaline (68a)*

N-*tertiarybutoxycarbonyl*-(R,S)-*valine (69)*

N-*tertiarybutoxycarbonyl*-(S)-*valine (69a)*

N-*tertiarybutoxycarbonyl*-(R,S)-*phenylglycine (70)*

N-*tertiarybutoxycarbonyl*-(R,S)-*phenylalanine (71)*

N-*tertiarybutoxycarbonyl*-(R,S)-2-*aminobutanoic acid (72)*

N-*tertiarybutoxycarbonyl*-(R,S)-*allylglycine (73)*

N-*tertiarybutoxycarbonyl*-(R,S)-*leucine (179)*

N-*tertiarybutoxycarbonyl*-(S)-*leucine (179a)*

N-*tertiarybutoxycarbonyl*-(2RS, 3RS)-*isoleucine (180)*

N-*tertiarybutoxycarbonyl*-(2S, 3S)-*isoleucine (180a)*

N-*tertiarybutoxycarbonyl*-(2S, 3R)-*isoleucine (180b)*

N-*tertiarybutoxycarbonyl*-(2R, 3R)-*isoleucine (180c)*

N-*tertiarybutoxycarbonyl*-(2R, 3S)-*isoleucine (180d)*

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl 2-[*(tertiarybutoxycarbonyl)*amino]acetate *(47)*

N-tertiarybutoxycarbonylglycine (**46**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 93% yield. M.S. 389 (M^+), 333 ($M^+ - C_4H_8$). Microanalysis: found C 70.84%, H 9.14%. $C_{23}H_{35}NO_4$ requires C 70.92%, H 9.06%. ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.6 Hz, 3H (ring CH_3); 1.18, s, 3H (CH_3CPh); 1.29, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 8H (methylene envelope); 3.05, d of d, *J* 5.9, 15.1 Hz, 1H (*pro-R* α-CH); 3.29, d of d, *J* 5.3, 15.1 Hz, 1H (*pro-S* α CH); 4.38, br. m, 1H (NH); 4.87, d of t, *J* 4.2, 10.7 Hz, 1H (HC-O); 7.1-7.4, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.64 (CH_3CPh); 22.66 (CH_3CPh); 26.15 (ring CH_2CHCPh); 28.22 (*t*Bu CH_3); 29.45 (ring CH_3); 31.13 (ring $CHCH_3$); 34.37 (ring CH_2CHCH_3); 39.28, (CMe_2Ph); 41.49 (ring CH_2C-O); 42.26 (α CH_2); 50.15 (ring CHCPh); 74.73 (H-C-O); 79.27 (CMe_3); 125.07,125.20, 127.79, 155.34 (Ar); 151.73 (*t*Boc C=O); 169.07 (ester C=O). ν_{max} 3410, 1725 cm^{-1}.

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-[*(tertiarybutoxycarbonyl)*amino]propanoate *(74)*

N-tertiarybutoxycarbonyl-(*R*,*S*)-alanine (**67**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 95% yield. Microanalysis: found C 71.22%, H 9.27%. $C_{24}H_{37}NO_4$ requires C 71.43%, H 9.24%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**74a**): F.A.B. M.S. : m/z 404 ($[M + H]^+$), 348 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.2 Hz, 3H (ring CH_3); 1.09, d, *J* 7.1 Hz, 3H (α CH_3); 1.20, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 8H (methylene envelope); 3.65, m, 1H (α CH); 4.49, d, *J* 7.2 Hz, 1H (NH); 4.81, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.1-7.4, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 18.44, (α CH_3); 21.75 (CH_3CPh); 23.88 (CH_3CPh); 26.47 (ring CH_2CHCPh); 28.41 (*t*Bu CH_3); 28.93 (ring CH_3); 31.26 (ring $CHCH_3$); 34.56 (ring CH_2CHCH_3); 39.54, (CMe_2Ph); 41.41 (ring CH_2C-O); 49.12 (α CH); 50.34 (ring CHCPh); 75.32 (H-C-O); 79.28 (CMe_3); 125.31,128.05, 154.83 (Ar); 151.7 (*t*Boc C=O); 172.18 (ester C=O).

Data for the 2-(*R*) diastereomer (**74b**): F.A.B. M.S. : m/z 404 ($[M + H]^+$), 348 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R (300 MHz) δ: 0.86, d, *J* 6.4 Hz, 3H (ring CH_3); 1.20, d, *J* 7.1 Hz, 3H (α CH_3); 1.23, s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 8H (methylene envelope); 3.96, m, 1H (α CH); 4.78, d, *J* 8.1 Hz, 1H (NH); 4.87, d of t, *J* 4.4, 10.7 Hz, 1H (HC-O); 7.1-7.4, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 18.00, (α CH_3); 21.71 (CH_3CPh); 26.15 (ring CH_2CHCPh); 26.99 (CH_3CPh); 27.62 (ring CH_3); 28.35 (*t*Bu CH_3); 31.32 (ring $CHCH_3$); 34.50 (ring CH_2CHCH_3); 40.06, (CMe_2Ph); 41.67 (ring CH_2C-O); 49.84 (α CH); 50.08 (ring CHCPh); 76.16 (H-C-O); 79.10 (CMe_3); 125.33, 125.52, 128.00, 154.84 (Ar); 150.96 (*t*Boc C=O); 172.18 (ester C=O).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (S)-2-*[(tertiarybutoxycarbonyl)amino]propanoate (74a)*

N-tertiarybutoxycarbonyl-(*S*)-alanine (**67a**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 82% yield. N.M.R. data : identical to the data quoted above for the 2-(*S*) diastereomer (**67a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]pentanoate (75)*

N-tertiarybutoxycarbonyl-(*R*,*S*)-norvaline (**68**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 98% yield. Microanalysis: found C 73.07%, H 9.47%. $C_{26}H_{41}NO_4$ requires C 72.35%, H 9.38%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**75a**): F.A.B. M.S. : m/z 432 ($[M + H]^+$), 376 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.80-0.95, complex, 6H (ring CH_3 and δ CH_3); 1.21, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.95-1.90, complex, 11H (methylene envelope); 2.05, d of t, *J* 3.2, 8.9 Hz, 1H (ring CH); 3.64, br. d of d, *J* 5.7, 13.8 Hz, 1H (α CH); 4.52, d, *J* 8.7 Hz, 1H (NH); 4.79, d of t, *J* 4.3, 10.8 Hz, 1H (HC-O); 7.15-7.35, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 13.68 (δ CH_3); 18.41 (β or γ CH_2); 21.72 (CH_3CPh); 24.08 (CH_3CPh); 26.36 (ring CH_2CHCPh); 28.31 (*t*Bu CH_3); 28.69 (ring CH_3); 31.18 (ring $CHCH_3$); 34.47 (ring CH_2CHCH_3); 39.45, (CMe_2Ph); 41.29 (ring

CH_2C-O); 50.24 (ring CHCPh); 53.10 (α CH); 75.35 (H-C-O); 79.13 (CMe_3); 125.20, 125.26, 127.96, 155.12 (Ar); 151.54 (*t*Boc C=O); 171.92 (ester C=O).

Data for the 2-(*R*) diastereomer (**75b**): F.A.B. M.S. : m/z 432 ($[M + H]^+$), 376 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.80-0.95, complex, 6H (ring CH_3 and δ CH_3); 1.23, s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.95-2.10, complex, 12H (methylene envelope); 3.97, br. d of d, *J* 8.2, 12.8 Hz, 1H (α CH); 4.72, d, *J* 9.3 Hz, 1H (NH); 4.85, d of t, *J* 4.3, 10.6 Hz, 1H (HC-O); 7.10-7.30, complex, 5H (ArH).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (S)-2-*[(tertiarybutoxycarbonyl)amino]*pentanoate *(75a)*

N-tertiarybutoxycarbonyl-(*S*)-norvaline (**68a**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 56% yield. N.M.R. data : identical to the data quoted above for the 2-(*S*) diastereomer (**75a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]*-3-methylbutanoate *(76)*

N-tertiarybutoxycarbonyl-(*R,S*)-valine (**69**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 88% yield. Microanalysis: found C 72.08%, H 9.38%. $C_{26}H_{41}NO_4$ requires C 72.35%, H 9.57%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**76a**): F.A.B. M.S. : m/z 432 ($[M + H]^+$), 376 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R (300 MHz) δ: 0.70, d, *J* 6.8 Hz, 3H (*i*Pr CH_3); 0.80, d, *J* 6.8 Hz, 3H (*i*Pr CH_3); 0.89, d, *J* 6.6 Hz, 3H (ring CH_3); 1.22, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.47, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 9H (methylene envelope); 3.53, d of d, *J* 3.6, 8.6 Hz, 1H (α CH); 4.78, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 4.86, d, *J* 8.6 Hz, 1H (NH); 7.1-7.4, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 17.35, (*i*Pr CH_3); 18.64 (*i*Pr CH_3); 21.75 (CH_3CPh); 24.64 (CH_3CPh); 26.47 (ring CH_2CHCPh); 28.28 (*t*Bu CH_3 and ring CH_3); 31.01 (ring $CHCH_3$); 31.25 (*i*Pr CH); 34.49 (ring CH_2CHCH_3); 39.52, (CMe_2Ph); 41.48 (ring CH_2C-O); 50.48 (ring CHCPh); 58.04 (α CH); 75.51 (H-C-O); 79.21 (CMe_3); 125.27,127.92, 155.28 (Ar); 151.22 (*t*Boc C=O); 171.46 (ester C=O).

Data for the 2-(*R*) diastereomer (**76b**): F.A.B. M.S. : m/z 432 ($[M + H]^+$), 376 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.82, d, *J* 6.9 Hz, 3H (*i*Pr CH_3); 0.83, d, *J* 6.5 Hz, 3H (*i*Pr CH_3); 0.91, d, *J* 6.8 Hz, 3H (ring CH_3); 1.24, s, 3H (CH_3CPh); 1.33, s, 3H (CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 9H (methylene envelope); 4.07, d of d, *J* 4.5, 9.5 Hz, 1H (α CH); 4.72-4.91, complex, 2H (NH & HC-O); 7.1-7.4, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 16.96, (*i*Pr CH_3); 19.35 (*i*Pr CH_3); 21.68 (CH_3CPh); 24.99 (CH_3CPh); 27.18 (ring CH_2CHCPh); 28.28 (*t*Bu CH_3); 28.94 (ring CH_3); 30.55 (*i*Pr CH); 31.33 (ring $CHCH_3$); 34.40 (ring CH_2CHCH_3); 40.12, (CMe_2Ph); 41.66 (ring CH_2C-O); 49.95 (ring CHCPh); 58.90 (α CH); 76.42 (H-C-O); 79.48 (CMe_3); 125.33, 125.52, 127.98, 155.38 (Ar); 150.50 (*t*Boc C=O); 171.07 (ester C=O).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (S)-2-*[(tertiarybutoxycarbonyl)amino]*-3-methylbutanoate *(76a)*

N-tertiarybutoxycarbonyl-(*S*)-valine (**69a**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 76% yield. N.M.R. data : identical to the data quoted above for the 2-(*S*) diastereomer (**76a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]*-2-phenylacetate *(77)*

N-tertiarybutoxycarbonyl-(*R*,*S*)-phenylglycine (**70**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 95% yield. Microanalysis: found C 74.81%, H 8.23%. $C_{29}H_{39}NO_4$ requires C 74.81%, H 8.44%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**77a**): F.A.B. M.S. : m/z 466 ($[M + H]^+$), 410 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.76, d, *J* 6.3 Hz, 3H (ring CH_3); 1.22, s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.45, s, 9H (*t*Bu CH_3); 2.00, d of t, *J* 2.8, 11.6 Hz, 1H (ring CH); 0.8-1.9, complex, 7H (methylene envelope); 4.34, d, *J* 7.1 Hz, 1H (α CH); 4.79, d of t, *J* 4.3, 10.6 Hz, 1H (HC-O); 5.46, d, *J* 7.1 Hz, 1H (NH); 6.9-7.4, complex, 10H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.54 (CH_3CPh); 23.73 (CH_3CPh); 26.73 (ring CH_2CHCPh); 28.22 (*t*Bu CH_3); 28.80 (ring CH_3); 31.07 (ring $CHCH_3$); 34.36 (ring CH_2CHCH_3); 39.49, (CMe_2Ph); 40.46 (ring CH_2C-O); 50.34 (ring CHCPh); 57.12 (α CH); 75.58 (H-C-O); 79.53

(CMe3); 125.28, 126.75, 127.92, 128.23, 137.41, 154.32 (Ar); 151.29 (*t*Boc C=O); 169.98 (ester C=O).

Data for the 2-(*R*) diastereomer (**77b**): F.A.B. M.S. : m/z 466 ($[M + H]^+$), 410 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.84, d, *J* 6.4 Hz, 3H (ring CH_3); 0.80, s, 3H (CH_3CPh); 1.00, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 1.0-1.7, complex, 7H (methylene envelope); 1.82, d of t, *J* 3.3, 11.9 Hz, 1H (ring CH); 4.79, d of t, *J* 4.4, 10.5 Hz, 1H (HC-O); 5.13, d, *J* 6.7 Hz, 1H (α CH); 5.52, d, *J* 6.7 Hz, 1H (NH); 7.0-7.4, complex, 10H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.62 (CH_3CPh); 23.77 (CH_3CPh); 27.25 (ring CH_2CHCPh); 28.28 (*t*Bu CH_3); 29.25 (ring CH_3); 31.31 (ring $CHCH_3$); 34.36 (ring CH_2CHCH_3); 39.97, (CMe_2Ph); 41.54 (ring CH_2C-O); 50.41 (ring CHCPh); 58.38 (α CH); 77.26 (H-C-O); 79.95 (CMe_3); 125.33, 125.59, 127.60, 127.86, 128.31, 128.69, 136.70, 154.57 (Ar); 149.99 (*t*Boc C=O); 169.42 (ester C=O).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tertiarybutoxycarbonyl)amino]-3-phenylpropanoate (60)

N-tertiarybutoxycarbonyl-(*R*,*S*)-phenylalanine (**71**) was esterified with (−)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 96% yield. Microanalysis: found C 75.08%, H 8.57%. $C_{30}H_{41}NO_4$ requires C 75.12%, H 8.62%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**60a**): F.A.B. M.S. : m/z 480 ($[M + H]^+$), 424 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.5 Hz, 3H (ring CH_3); 1.18, s, 3H (CH_3CPh); 1.26, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.8-1.9,

complex, 7H (methylene envelope); 2.05, d of t, *J* 3.5 *J* 11.2 Hz, 1H (ring CH); 2.62, d of d, *J* 6.4 *J* 13.9 Hz, 1H (β CH); 2.87, d of d, *J* 5.8 *J* 13.9 Hz, 1H (β CH); 3.87, d of d, *J* 6.2, 14.3 Hz, 1H (α CH); 4.54, d, *J* 8.3 Hz, 1H (NH); 4.74, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.0-7.4, complex, 10H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.72 (CH_3CPh); 23.85 (CH_3CPh); 26.37 (ring CH_2CHCPh); 28.31 (*t*Bu CH_3); 28.90 (ring CH_3); 31.20 (ring $CHCH_3$); 34.46 (ring CH_2CHCH_3); 37.70 (β CH_2); 39.44, (CMe_2Ph); 41.39 (ring CH_2C-O); 50.21 (ring CHCPh); 54.16 (α CH); 75.80 (H-C-O); 79.30 (CMe_3); 125.16, 126.63, 128.04, 128.15, 129.47, 136.49, 154.80 (Ar); 151.66 (*t*Boc C=O); 170.91 (ester C=O).

Data for the 2-(*R*) diastereomer (**60b**): F.A.B. M.S. : m/z 480 ($[M + H]^+$), 424 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.81, d, *J* 6.6 Hz, 3H (ring CH_3); 1.18, s, 3H (CH_3CPh); 1.27, s, 3H (CH_3CPh); 1.40, s, 9H (*t*Bu CH_3); 1.0-2.1, complex, 8H (methylene envelope); 2.84, d of d, *J* 7.5, 13.8 Hz, 1H (β CH); 2.98, d of d, *J* 5.3, 13.8 Hz, 1H (β CH); 4.04, br. d of d, *J* 7.5, 13.2 Hz, 1H (α CH); 4.56, d, *J* 7.1 Hz, 1H (NH); 4.84, d of t, *J* 4.4, 10.7 Hz, 1H (HC-O); 7.0-7.4, complex, 10H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.49 (CH_3CPh); 26.09 (CH_3CPh); 26.60 (ring CH_2CHCPh); 26.92 (ring CH_3); 28.14 (*t*Bu CH_3); 31.07 (ring $CHCH_3$); 34.24 (ring CH_2CHCH_3); 37.25 (β CH_2); 39.61, (CMe_2Ph); 41.23 (ring CH_2C-O); 49.83 (ring CHCPh); 54.87 (α CH); 75.78 (H-C-O); 79.26 (CMe_3); 125.19, 126.44, 127.79, 128.11, 129.35, 136.59, 154.51 (Ar); 150.89 (*t*Boc C=O); 170.30 (ester C=O).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]*butanoate (78)

N-tertiarybutoxycarbonyl-(*R,S*)-2-aminobutanoic acid (**72**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 55% yield. Microanalysis: found C 71.64%, H 9.06%. $C_{25}H_{39}NO_4$ requires C 71.91%, H 9.41%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**78a**): F.A.B. M.S. : m/z 418 ($[M + H]^+$), 362 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.76, t, *J* 7.4 Hz 3H, (γ CH_3); 0.87, d, *J* 6.8 Hz, 3H (ring CH_3); 1.21, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, 10H (methylene envelope); 3.57, br. d of d, *J* 7.0, 13.3 Hz, 1H (α CH); 4.63, d, *J* 7.7 Hz, 1H (NH); 4.80, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.10-7.30, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 9.23 (γ CH_3); 21.71 (CH_3CPh); 24.07 (CH_3CPh); 25.38 (β CH_2); 26.35 (ring CH_2CHCPh); 28.30 (*t*Bu CH_3); 28.64 (ring CH_3); 31.18 (ring $CHCH_3$); 34.45 (ring CH_2CHCH_3); 39.44, (CMe_2Ph); 41.37 (ring CH_2C-O); 50.27 (ring CHCPh); 54.18 (α CH); 75.30 (H-C-O); 79.15 (CMe_3); 125.24, 127.94, 155.05 (Ar); 151.45 (*t*Boc C=O); 171.67 (ester C=O).

Data for the 2-(*R*) diastereomer (**78b**): F.A.B. M.S. : m/z 418 ($[M + H]^+$), 362 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.86, t, *J* 7.4 Hz 3H, (γ CH_3); 0.85, d, *J* 6.4 Hz, 3H (ring CH_3); 1.23, s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 0.7-2.1, complex, 10H (methylene envelope); 3.93, br. d of d, *J* 7.4, 12.6 Hz, 1H (α CH); 4.76, d, *J* 8.1 Hz, 1H (NH); 4.86, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.10-7.30, complex, 5H (ArH).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]*pent-4-enoate (79)

N-tertiarybutoxycarbonyl-(*R*,*S*)-allylglycine (**73**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 76% yield. Microanalysis: found C 72.43%, H 8.80%. $C_{26}H_{39}NO_4$ requires C 72.69%, H 9.15%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**79a**): F.A.B. M.S. : m/z 430 ($[M + H]^+$), 374 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.4 Hz, 3H (ring CH_3); 1.21 s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.8-2.4, complex, 10H (methylene envelope); 3.64, br. d of d, *J* 6.1, 13.2 Hz, 1H (α CH); 4.66, d, *J* 7.7 Hz, 1H (NH); 4.81, d of t, *J* 4.4, 10.7 Hz, 1H (HC-O); 4.98-5.04, complex, 2H (CH_2=CH); 5.45-5.60, complex, 1H (CH=CH_2); 7.17-7.30, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.73 (CH_3CPh); 23.82 (CH_3CPh); 26.31 (ring CH_2CHCPh); 28.29 (*t*Bu CH_3); 28.85 (ring CH_3); 31.18 (ring $CHCH_3$); 34.44 (ring CH_2CHCH_3); 36.38 (CH_2C=C); 39.42, (CMe_2Ph); 41.42 (ring CH_2C-O); 50.26 (ring CHCPh); 52.59 (α CH); 75.55 (H-C-O); 79.29 (CMe_3); 118.45 (CH_2=C); 125.23, 127.97, 154.87 (Ar); 132.59 (CH=CH_2); 151.60 (*t*Boc C=O); 170.98 (ester C=O).

Data for the 2-(*R*) diastereomer (**79b**): F.A.B. M.S. : m/z 430 ($[M + H]^+$), 374 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.86, d, *J* 6.5 Hz, 3H (ring CH_3); 1.23, s, 3H (CH_3CPh); 1.33, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.8-2.4, complex, 10H (methylene envelope); 3.98, br. d of d, *J* 7.5, 12.5 Hz, 1H (α CH); 4.71, d, *J* 8.3 Hz, 1H (NH); 4.86, d of t, *J* 4.3, 10.6 Hz, 1H (HC-O); 5.03-

5.15, complex, 1H, (CH_2=CH); 5.54-5.71, complex, 1H, (CH_2=CH); 7.1-7.4, complex, 5H (ArH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2S,3S)-2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (117a)

N-tertiarybutoxycarbonyl(2*S*,3*S*)isoleucine (**180a**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 48% yield. M.S. 445 (M^+), 389 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{44}NO_4$ ($[M + H]^+$) 446.327, found 446.324. ^{1}H-N.M.R. (300 MHz) δ: 0.76, d, *J* 6.8 Hz, 3H (γ CH_3); 0.81, t, *J* 7.4 Hz, 3H (δ CH_3); 0.87, d, *J* 6.5 Hz, 3H (ring CH_3); 1.22, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.47, s, 9H (*t*Bu CH_3); 0.90-2.10, complex, 11H (methylene envelope); 3.53, d of d, *J* 3.7, 8.2 Hz, 1H (α CH); 4.81, d of t, *J*-4.0, 8.3 Hz, 1H (HC-O); 4.93, d, *J*-8.2 Hz, 1H (NH); 7.10-7.35, complex, 5H (ArH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2S,3R)-2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (117b)

N-tertiarybutoxycarbonyl-(2*S*,3*R*)-isoleucine (**180b**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 61% yield. M.S. 445 (M^+), 389 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{44}NO_4$ ($[M + H]^+$) 446.327, found 446.328. ^{1}H-N.M.R. (300 MHz) δ: 0.66, d, *J* 6.9 Hz, 3H (γ CH_3); 0.75-0.90, complex, 6H, (δ CH_3 and ring CH_3); 1.22, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.47, s, 9H

(*t*Bu CH_3); 0.90-2.10, complex, 11H (methylene envelope); 3.66, d of d, *J* 3.3, 8.9 Hz, 1H (α CH); 4.79, d of t, *J* 4.4, 10.8 Hz, 1H (HC-O); 4.82, d, *J* 8.9 Hz, 1H (NH); 7.10-7.35, complex, 5H (ArH).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (2R,3R)-2-*[(tertiarybutoxycarbonyl)amino]*-3-methylpentanoate (117c)

N-tertiarybutoxycarbonyl-(2*R*,3*R*)-isoleucine (**180c**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 54% yield. M.S. 445 (M^+), 389 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{44}NO_4$ ($[M + H]^+$) 446.327, found 446.324. ^{1}H-N.M.R. (300 MHz) δ: 0.80-0.95, complex, 9H, (ring CH_3, γ CH_3 and δ CH_3); 1.25, s, 3H (CH_3CPh); 1.33, s, 3H (CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 0.95-2.05, complex, 11H (methylene envelope); 4.13, d of d, *J* 4.8, 9.3 Hz, 1H (α CH); 4.81, d, *J* 9.3 Hz, 1H (NH); 4.85, d of t, *J* 4.2, 10.5 Hz, 1H (HC-O); 7.10-7.35, complex, 5H (ArH).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (2R,3S)-2-*[(tertiarybutoxycarbonyl)amino]*-3-methylpentanoate (117d)

N-tertiarybutoxycarbonyl-(2*R*,3*S*)-isoleucine (**180d**) was esterified with (–)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 66% yield. M.S. 445 (M^+), 389 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{44}NO_4$ ($[M + H]^+$) 446.327, found 446.324. ^{1}H-N.M.R. (300 MHz) δ: 0.78, d, *J* 6.8 Hz, 3H (γ CH_3); 0.85, d, *J* 6.3 Hz, 3H (ring CH_3); 0.91, t, *J* 7.4 Hz, 3H (δ CH_3); 1.24, s, 3H (CH_3CPh); 1.33, s, 3H

(CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 1.00-2.00, complex, 11H (methylene envelope); 4.26, d of d, *J* 3.7, 8.2 Hz, 1H (α CH); 4.70-4.90, complex, 2H (HC-O, NH); 7.05-7.35, complex, 5H (ArH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2RS, 3RS)-2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (117)

An equimolar mixture of (2*S*, 3*S*), (2*S*, 3*R*), (2*R*, 3*R*) and (2*R*, 3*S*)-*N*-tertiarybutoxycarbonyl-isoleucine (**180**) was esterified with (−)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 53% yield. Microanalysis: found C 72.36%, H 9.70%. $C_{27}H_{43}NO_4$ requires C 72.77%, H 9.73%. ^{1}H-N.M.R. (300 MHz) : indicated that an equimolar mixture of the four isoleucinates (**117a**), (**117b**), (**117c**) and (**117d**) was formed.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (S)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (48)

A suspension of *N*-bromosuccinimide (56mg, 0.314 mmol) in a refluxing solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]acetate (**47**) (121mg, 0.311 mmol) in dry carbon tetrachloride (5ml) was irradiated for ten minutes with a 300 W sun lamp at a distance of 10 cm. After simultaneously ending heating and irradiation, the reaction mixture was cooled in an ice bath then filtered. The carbon tetrachloride was evaporated *in vacuo* to give the *title compound* as a colourless oil (144mg, 99%) which later solidified. Due to

the instability of this compound, characterization was possible by ^{1}H-N.M.R. and ^{13}C-N.M.R. only. ^{1}H-N.M.R. (300 MHz, CCl_4) δ: 0.94, d, *J* 6.5 Hz, 3H (ring CH_3); 1.20 s, 3H (CH_3CPh); 1.29, s, 3H (CH_3CPh); 1.50, s, 9H (*t*Bu CH_3); 0.85-2.15, complex, 8H (methylene envelope); 4.82, d of t, *J* 4.2, 10.8 Hz, 1H (HC-O); 4.87, d, *J* 10.7 Hz, 1H (α CH); 5.45, br. d, *J* 10.7 Hz, 1H (NH); 7.00-7.30, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz, CCl_4) δ: 21.72 (CH_3CPh); 25.94 (ring CH_2CHCPh); 28.02 (*t*Bu CH_3); 30.01 (ring CH_3); 31.06 (ring $CHCH_3$); 34.36 (ring CH_2CHCH_3); 39.02, (CMe_2Ph); 39.99 (ring CH_2C-O); 50.34 (ring CHCPh); 53.70 (α CH); 75.25 (H-C-O); 80.59 (CMe_3); 124.74, 125.14, 125.44, 127.59, 127.78 (Ar); 150.76 (*t*Boc C=O);164.60 (ester C=O).

(1R, 2S, 5R)-2-(1-methylethyl)-5-methylcyclohexyl (S)-2-[(tertiarybutoxycarbonyl)amino]acetate (80)

N-tertiarybutoxycarbonylglycine was esterified with (–)-menthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 98% yield. M.S. 313 (M^+), 257 ($M^+ - C_4H_8$). Exact mass calculated for $C_{13}H_{24}NO_4$ ($[M + H]^+ - C_4H_8$) 258.170, found 258.168. Microanalysis: found C 64.27%, H 9.56%. $C_{17}H_{31}NO_4$ requires C 65.14%, H 9.97%. ^{1}H-N.M.R. (300 MHz) δ: 0.75, d, *J* 7.0 Hz, 3H (ring CH_3); 0.89, d, *J* 6.9 Hz, 3H (CH_3CPh); 0.91, d, *J* 6.6 Hz, 3H (CH_3CPh); 1.45, s, 9H (*t*Bu CH_3); 0.8-2.2, complex, 9H (methylene envelope); 3.89, d, *J* 5.4 Hz, 2H (α-CH_2); 4.75, d of t, *J* 4.4, 10.9 Hz, 1H (HC-O); 5.03, br. m, 1H (NH).

(1R, 2S, 5R)-2-*(1-methylethyl)*-5-methylcyclohexyl
(S)-2-*[(tertiarybutoxycarbonyl)amino]*-2-bromoacetate *(81)*

A suspension of *N*-bromosuccinimide (56.5 mg, 0.317 mmol) in a refluxing solution of (1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]acetate (**80**) (98.5mg, 0.314 mmol) in dry carbon tetrachloride (4ml) was irradiated for ten minutes with a 300W sun lamp at a distance of 10 cm. After simultaneously ending heating and irradiation, the reaction mixture was cooled in an ice bath then filtered.. The carbon tetrachloride was evaporated *in vacuo* to give the *title compound* as a colourless oil (112 mg, 0.305 mmol, 91%). Due to the instability of this compound, characterization was possible by ^{1}H-N.M.R. only. ^{1}H-N.M.R. (300 MHz, CCl_4) δ: 0.78(4), 0.77(6), each d, *J* 6.9 Hz, ratio *ca.* 1:1, total 3H (ring CH_3); 0.91, 0.92, each d, *J* 7.0 Hz, ratio *ca.* 1:1, total 3H (*gem.* CH_3); 0.94, 0.97, each d, *J* 9.3 Hz, ratio *ca.* 1:1, total 3H (*gem.* CH_3); 1.48, br. s, 9H (*t*Bu CH_3); 0.75-2.15, complex, 9H (methylene envelope); 4.67, 4.73, each d of t, *J* 4.4, 11.0 Hz, ratio *ca.* 1:1, total 1H (HC-O); 5.74, br. d, *J* 10.6 Hz, 1H (NH); 6.17, 6.18, each d, *J* 10.6 Hz, ratio *ca.* 1:1, total 1H (α CH).

(1R, 2S, 5R)-2-*(1-methylethyl)*-5-methylcyclohexyl
2-*[(tertiarybutoxycarbonyl)imino]*acetate *(82)*

To a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**81**) (116 mg, 0.297 mmol) in anhydrous ether cooled to 0°C was added triethylamine (41 µl, 0.297 mmol). A white precipitate was formed immediately. Stirring was continued for one minute at 0°C and a further ten minutes at room temperature. The mixture was filtered and the filtrate concentrated *in*

vacuo to give the *title compound* (85 mg, 0.273 mmol, 92%). Due to the instability of this compound, characterization was possible by ^{1}H-N.M.R. only. ^{1}H-N.M.R. (60 MHz, $CDCl_3$) δ: 0.60-1.13, complex, 9H (ring CH_3, *gem*. CH_3, *gem*. CH_3); 1.53, s, 9H (*t*Bu CH_3); 1.13-2.30, complex, 9H (methylene envelope); 4.67, d of t, *J* 4, 10 Hz, 1H (HC-O); 6.17, br. s, 1H (α CH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)imino]acetate (49)

Following the procedure used for (**82**), (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (131 mg, 0.280 mmol) was treated with triethylamine (39 µl, 0.280 mmol) in anhydrous ether (5 ml) to give the *title compound* (79 mg, 0.203 mmol, 73%). Due to the instability of this compound, characterization was possible by ^{1}H-N.M.R. only. ^{1}H-N.M.R. (60 MHz, $CDCl_3$) δ: 0.90, d, *J* 5 Hz, 3H (ring CH_3); 1.23 s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.55, s, 9H (*t*Bu CH_3); 0.85-2.30, complex, 8H (methylene envelope); 4.95, d of t, *J* 4, 10 Hz, 1H (HC-O); 6.68, br. s, 1H (α CH); 6.90-7.30, complex, 5H (ArH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]propanoate (84)

Methylmagnesium iodide (335 µl of a 1.01 M solution in diethylether, 0.338 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-

5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (72 mg, 0.154 mmol, one equivalent) in anhydrous ether (2.6 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature. The now homogeneous solution was quenched by addition of excess saturated ammonium chloride solution. More ether and water were added, the layers separated, and the ether layer washed twice with water. The ether layer was dried over anhydrous magnesium sulphate and the ether evaporated *in vacuo*. Chromatography on silica gave 45 mg (0.112 mmol, 72%) of the *title compound*. ^{1}H-N.M.R. and ^{13}C-N.M.R.: detected only (1*R*,2*S*,5*R*)-2-(1-methyl1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]propanoate (**74a**). H.P.L.C. analysis detected one component only. This component coeluted with the authentic 2-(*S*) diastereomer (**74a**).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pentanoate (85)

n-Propylmagnesium bromide (325 µl of a 1.02 M solution in diethylether, 0.327 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (70 mg, 0.149 mmol, one equivalent) in anhydrous ether (2.5 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 54 mg (0.125 mmol, 84%) of the *title*

compound. ^{1}H-N.M.R. and ^{13}C-N.M.R. : Detected only (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]propanoate (**75a**). H.P.L.C. analysis detected two components in a 97.5 : 2.5 ratio. The major, first-eluting component coeluted with the authentic 2-(*S*) diastereomer (**75a**) and the minor, second-eluting component coeluted with the authentic 2-(*R*) diastereomer (**75b**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]-3-methylbutanoate (86)*

Isopropylmagnesium iodide (490 µl of a 0.81 M solution in diethylether, 0.399 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (85 mg, 0.181 mmol, one equivalent) in anhydrous ether (2.6 ml) cooled to −78°C. The reaction mixture was stirred for a further two hours at −78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 40 mg (0.093 mmol, 51%) of the *title compound*. ^{1}H-N.M.R. and ^{13}C-N.M.R.: Detected only (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]-3-methylbutanoate (**76a**). H.P.L.C. analysis detected one component only. This component coeluted with the authentic 2-(*S*) diastereomer (**76a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-*methylcyclohexyl* 2-*[(tertiarybutoxycarbonyl)amino]*-2-*phenylacetate (87)*

Phenylmagnesium bromide (450 µl of a 1.28 M solution in diethylether, 0.450 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (122 mg, 0.260 mmol, one equivalent) in anhydrous ether (4.3 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 100 mg (0.213 mmol, 82%) of the *title compound*. ^{1}H-N.M.R. and ^{13}C-N.M.R.: Detected only (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]-2-phenylacetate (**77a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-*methylcyclohexyl* 2-*[(tertiarybutoxycarbonyl)amino]*-3-*phenylpropanoate (88)*

Benzylmagnesium bromide (515 µl of a 0.82 M solution in diethylether, 0.442 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (90 mg, 0.192 mmol, one equivalent) in anhydrous ether (3.2 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 55 mg (0.111 mmol, 58%) of the *title*

compound. ^{1}H-N.M.R. and ^{13}C-N.M.R.: Detected only (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]-3-phenyl-propanoate (**60a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-*methylcyclohexyl* 2-*[(tertiarybutoxycarbonyl)amino]butanoate (89)*

Ethylmagnesium bromide (345 µl of a 0.98 M solution in diethylether, 0.337 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (72 mg, 0.153 mmol, one equivalent) in anhydrous ether (2.6 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 53 mg (0.122 mmol, 82%) of the *title compound*. ^{1}H-N.M.R. and ^{13}C-N.M.R. : Detected only (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]butanoate (**72a**). H.P.L.C. analysis detected two components in a 97.5 : 2.5 ratio. The major, first-eluting component coeluted with the authentic 2-(*S*) diastereomer (**72a**) and the minor, second-eluting component coeluted with the authentic 2-(*R*) diastereomer (**72b**).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]but-3-enoate (90)

Vinylmagnesium bromide (430 µl of a 1.00 M solution in tetrahydrofuran, 0.431 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (85 mg, 0.181 mmol, one equivalent) in anhydrous tetrahydrofuran (3.5 ml) cooled to −20°C. The reaction mixture was stirred for a further two hours at −20°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave the *title compound* in 52% yield. H.P.L.C. analysis showed two fractions in a 76.5:25.5 ratio. Small samples of each fraction were isolated by preparative H.P.L.C. :

Data for the major, first-eluting fraction (**90a**) : M.S. 415 (M^+), 359 ($M^+ - C_4H_8$). Exact mass calculated for $C_{25}H_{38}NO_4$ ($[M + H]^+$) 416.280, found 416.285. ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.5 Hz, 3H (ring CH_3); 1.20 s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.47, s, 9H (*t*Bu CH_3); 0.9-2.2, complex, 10H (methylene envelope); 4.07, br. m, 1H (α CH); 4.70, d, *J* 7.8 Hz, 1H (NH); 4.83, d of t, *J* 4.4, 10.7 Hz, 1H (HC-O); 5.11, d, *J* 10.4 Hz, 1H (*cis* HCH=CH); 5.12, d, *J*17.1 Hz, 1H (*trans* HCH=CH); 5.59, d of d of d, *J* 5.0, 10.4, 17.1 Hz, 1H ($CH=CH_2$); 7.10-7.30, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.73 (CH_3CPh); 23.38 (CH_3CPh); 26.26 (ring CH_2CHCPh); 28.31 (*t*Bu CH_3); 29.19 (ring CH_3); 31.21 (ring $CHCH_3$); 34.43 (ring CH_2CHCH_3); 39.40, (CMe_2Ph); 41.17 (ring CH_2C-O); 50.28 (ring CHCPh); 55.52 (α CH); 75.69 (H-C-O); 79.53 (CMe_3); 116.49 ($CH_2=C$); 125.23, 125.33, 128.07, 154.87 (Ar); 132.86 ($CH=CH_2$); 151.61 (*t*Boc C=O); 169.62 (ester C=O).

Data for the minor, second-eluting fraction (**90b**) : M.S. 415 (M^+), 359 ($M^+ - C_4H_8$). Exact mass calculated for $C_{25}H_{38}NO_4$ ($[M + H]^+$) 416.280, found 416.281. ^{1}H-N.M.R. (300 MHz) δ: 0.86, d, *J* 6.3 Hz, 3H (ring CH_3); 1.23, s, 3H (CH_3CPh); 1.31, s, 3H (CH_3CPh); 1.44, s, 9H (*t*Bu CH_3); 0.75-2.05, complex, 8H (methylene envelope); 4.54, br. m, 1H (α CH); 4.86, d of t, *J* 4.3, 10.6 Hz, 1H (HC-O); 4.99, d, *J* 7.6 Hz, 1H (NH); 5.20, br. d, *J* 10.3 Hz, 1H (*cis* HCH=CH); 5.29, br. d, *J* 17.4 Hz, 1H (*trans* HCH=CH); 5.71, d of d of d, *J* 5.7, 10.3, 17.4 Hz, 1H (HCH=CH); 7.10-7.30, complex, 5H (ArH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]butanoate (96)

A *ca.* 75 : 25 2-(*S*) : 2-(*R*) mixture (1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]but-3-enoate (**90**) (49 mg) was reduced over 10% Pd/C (35 mg) in methanol (5 ml) under one atmosphere of hydrogen for sixteen hours. The catalyst was removed by filtration and the methanol evaporated *in vacuo* to give the *title compound* (44 mg, 88%) as a *ca.* 75:25 2-(*S*) : 2-(*R*) mixture of diastereomers (determined by H.P.L.C. analysis; correlation was made with the authentic 2-(*S*) and 2-(*R*) (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]butanoates (**78a**) and (**78b**)). ^{1}H-N.M.R. : Comparison to the spectra of the authentic compounds (**78a**) and (**78b**) indicated that a *ca.* 75 : 25 mixture of these two compounds was present.

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-*methylcyclohexyl* 2-*[(tertiarybutoxycarbonyl)amino]pent-4-enoate (91)*

Allylmagnesium bromide (450 µl of a 0.76 M solution in diethylether, 0.341 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (73 mg, 0.155 mmol, one equivalent) in anhydrous ether (2.6 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 45 mg (0.104 mmol, 67%) of the *title compound*. ^{1}H-N.M.R. and ^{13}C-N.M.R. : indicated that a mixture of the 2-(*S*) and 2-(*R*) (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-4-enoates (**79a**) and (**79b**) had been formed. H.P.L.C. analysis detected two components in a 78.5 : 21.5 ratio. The major, first-eluting component coeluted with the authentic 2-(*S*) diastereomer (**79a**) and the minor, second-eluting component coeluted with the authentic 2-(*R*) diastereomer (**79b**).

N-*benzoyl*-(R,S)-*alanine methyl ester (108)*

Thionyl chloride (1.79 g, 15 mmol) was slowly added dropwise to ice-cooled, magnetically stirred methanol (10 ml). (*R,S*)-alanine (1.00 g, 11.22 mmol) was added and the homogeneous solution left to stand for sixteen hours. The methanol was then evaporated *in vacuo*, and the solid residue dissolved in water (38 ml). Potassium bicarbonate (5.62 g, 56.2 mmol) was cautiously added, followed by ethyl acetate (25 ml. A

solution of benzoyl chloride (1.73 g, 12.32 mmol) in ethyl acetate (12.5 ml) was slowly added to the rapidly stirred mixture. Stirring was continued for a further two hours. The layers were then separated and the organic layer successively washed with dilute hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulphate and the ethyl acetate evaporated*in vacuo* to yield the *title compound* as a white solid which was recrystallized from ethyl acetate/light petroleum. Yield = 2.12 g, ~~10.24g,~~ 91%. M.P. = 80-82°C. Lit.[112]: 80.5-81.5°C. ^{1}H-N.M.R. (60 MHz) δ: 1.50, d, *J* 7 Hz, 3H (β CH_3); 3.73, s, 3H (CH_3O); 4.75, m, 1H (α CH); 6.90, br. s, 1H (NH); 7.3-7.9, complex, 5H (ArH).

N-*benzoyl*-(S)-*alanine methyl ester (108a)*

Synthesized by the method used for *N*-benzoyl-(*R*,*S*)-alanine methyl ester (**108**). Yield = 89%. ^{1}H-N.M.R. data identical to (**108**).

N-*benzoyl*-(S)-*alanine methyl ester (108a)*

#1 : Hydrolysis time of 1 hour.

(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]propanoate (**74a**) (178 mg, 0.441 mmol) was dissolved in trifluoroacetic acid (1 ml) and the solution was left to stand for fifteen minutes. 6N HCl (2 ml) was then added, and the homogeneous solution was refluxed for one hour. After cooling to room temperature, water was added and the resultant solution washed with chloroform (2X). The aqueous layer was evaporated to dryness *in vacuo*, leaving 16 mg (0.097 mmol, 22%) of the mixed alanine hydochloride/hydrotrifluoroacetate as a yellow-green amorphous solid.

Without purification, the crude hydrolysate was derivatized by the procedure used in the synthesis of *N*-benzoyl-(*R,S*)-alanine methyl ester (**108**) to yield the *title compound* (17 mg, 0.082 mmol, 19% overall yield from (**74a**)). ^{1}H-N.M.R. : identical to that of authentic *N*-benzoyl-(*S*)-alanine methyl ester (**108a**). Chiral H.P.L.C. analysis did not detect any of the the (*R*) enantiomer.

#2 : Hydrolysis time of 2.5 hours.

(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]propanoate (**74a**) (224 mg, 0.555 mmol) was hydrolyzed by the procedure detailed above in "#1" except hydrolysis was carried out for 2.5 hours. Obtained 44 mg (0.268 mmol, 48%) of the mixed alanine hydochloride/hydrotrifluoroacetate as a yellow-green amorphous solid. Without purification, the crude hydrolysate was derivatized by the method used for *N*-benzoyl-(*R,S*)-alanine methyl ester (**108**) to yield the *title compound* (45 mg, 0.217 mmol, 39% overall yield from (**74a**)). ^{1}H-N.M.R. : identical to that of authentic *N*-benzoyl-(*S*)-alanine methyl ester (**108**). Chiral H.P.L.C. analysis did not detect any of the the (*R*) enantiomer.

#3 : Hydrolysis time of 15 hours.

(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]propanoate (**74a**) (111 mg, 0.275 mmol) was hydrolyzed by the procedure detailed above in "#1" except hydrolysis was carried out for 15 hours. Obtained 35 mg (0.212 mmol, 77%) of the mixed alanine hydochloride/hydrotrifluoroacetate as a yellow-green amorphous solid which was purified by ion exchange chromatography on Amberlite

1R-120 (H). The free (*S*)-alanine (19 mg, 0.212 mmol) was derivatized by the method used for *N*-benzoyl-(*R,S*)-alanine methyl ester (**108**) to yield the *title compound* (43 mg, 0.208 mmol, 75% overall yield from (**74a**)). ^{1}H-N.M.R. : identical to that of authentic *N*-benzoyl-(*S*)-alanine methyl ester (**108a**). Chiral H.P.L.C. analysis did not detect any of the the (*R*) enantiomer.

(S)-*alanine (106)*

(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]propanoate (**74a**) (239 mg, 0.592 mmol) was hydrolyzed by the procedure in "# 1" except hydrolysis was carried out for 15 hours. Obtained 92 mg (0.560 mmol, 95%) of the mixed alanine hydochloride/hydrotrifluoroacetate as a yellow-green amorphous solid which was purified by ion exchange chromatography on Amberlite 1R-120 (H). The free (*S*)-alanine (38 mg, 0.427 mmol, 72%) was analyzed by polarimetry. $[\alpha]_D^{24}$ = +16.1 ± 0.9°, C=3, 1N HCl. Lit.[75]: +14.7°, C=5.8, 1N HCl. A solution of authentic (*S*)-alanine was made up to a concentration of 3 g/100 ml in 1N HCl. $[\alpha]_D^{24}$ = +16.4 ± 0.9°, C=3, 1N HCl. M.P. 293-294°C (dec.); lit.[75] 297°C (dec.). ^{1}H-N.M.R. (60 MHz) δ : 1.75, d, *J* 7 Hz, 3H (α CH_3); 5.05, q, *J* 7 Hz, 1H (α CH).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl [(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (118)

#1 : 2.2 equivalents of Grignard reagent, reaction quenched at room temp. *sec*-Butylmagnesium bromide (377 µl of a 0.80 M solution in diethylether, 0.301 mmol, 2.2 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (64 mg, 0.137 mmol, one equivalent) in anhydrous ether (2.3 ml) cooled to –78°C. The reaction mixture was stirred for a further two hours at –78°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**84**). Chromatography on silica gave 23 mg (0.052 mmol, 38%) of the *title compound*. ^{1}H-N.M.R. : correlation with the spectra of the authentic compounds (**117a**) and (**117b**) indicated that a 1:1 mixture of (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2*S*, 3*S*)- and (2*S*, 3*R*)-[(tertiarybutoxycarbonyl)amino]-3-methyl-pentanoate (**117a**) and (**117b**) had been formed. H.P.L.C. analysis detected three components in a 95.0 : 2.3 : 2.7 ratio. The major, first-eluting component coeluted with the authentic (2*S*, 3*S*) and (2*S*, 3*R*) diastereomers (**117a**) and (**117b**). The second and third-eluting components coeluted with the authentic (2*R*, 3*S*) and (2*R*, 3*R*)diastereomers (**117d**) and (**117c**).

#2 : 3 equivalents of Grignard reagent, reaction quenched at –78°C. *sec*-Butylmagnesium bromide (1.11 ml of a 0.80 M solution in diethylether, 0.886 mmol, 3 equivalents) was added dropwise, over a period of thirty minutes, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-

butoxycarbonyl)amino]-2-bromoacetate (**48**) (134 mg, 0.295 mmol, one equivalent) in anhydrous ether (4.9 ml) cooled to −78°C. The reaction mixture was stirred for a further two hours at −78°C. Excess saturated ammonium chloride solution was then added. The cold bath was removed and the reaction mixture allowed to warm to room temperature, followed by workup as for (**48**). Chromatography on silica gave 67 mg (0.150 mmol, 51%) of the *title compound*. ^{1}H-N.M.R. : correlation with the spectra of the authentic compounds (**117a**) and (**117b**) indicated that a 1:1 mixture of (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2*S*, 3*S*)- and (2*S*, 3*R*)-[(tertiarybutoxycarbonyl)amino]-3-methyl-pentanoate (**117a**) and (**117b**) had been formed. H.P.L.C. analysis detected three components in a 95.3 : 2.0 : 2.7 ratio. The major, first-eluting component coeluted with the authentic (2*S*, 3*S*) and (2*S*, 3*R*) diastereomers (**117a**) and (**117b**). The second and third-eluting components coeluted with the authentic (2*R*, 3*S*) and (2*R*, 3*R*)diastereomers (**117d**) and (**117c**).

BROMINATION OF (47) WITH *N*-BROMOSUCCINIMIDE AT ROOM TEMPERATURE

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]acetate (**47**) (62 mg, 0.160 mmol) and *N*-bromosuccinimide (29 mg) in carbon tetrachloride (4 ml) at room temperature were irradiated for thirty minutes with a 300 W sun lamp at a distance of 10 cm. The mixture was filtered and analyzed directly by ^{1}H-N.M.R. spectroscopy. ^{1}H-N.M.R. (300 MHz, CCl_4) : contained signals due to the bromide (**48**) and the following signals : δ 0.90, d, *J* 6.3 Hz, 1.15, s, 1.24, s. The remaining signals due to this minor compound were obscured by the signals due to (**48**).

tri-n-butyltin deuteride (177)

Prepared according to method of Kuivila *et al*[89] for the corresponding hydride, using lithium aluminium deuteride (99 atom%). Yield = 69%, b.p. 55-60°C @ 0.1 mm Hg. (lit.[23] 68-74°C, 0.3 mm Hg).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (S)-2-*[(tertiarybutoxycarbonyl)amino]*-2-deuterioacetate *(128a)*

1 : Solvent : ether, [**48**] = 70 mM, 1.1 equivalents *n*-Bu_3SnD, -78°C → R.T. Tri-*n*-butyltin deuteride (105 µl, 0.387 mmol, 1.1 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (161 mg, 0.344 mmol, 1.0 equivalent) in anhydrous ether (5.00 ml) cooled to –78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (117 mg, 0.300 mmol, 85%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.050, d, *J* 5.4 Hz 0.85 H; δ 3.289, br. d, *J* 4.7 Hz, 0.15 H. ^{13}C-N.M.R. (75.5 MHz) : identical to that of (**47**) except for : δ 42.05, 1:1:1 triplet, *J* 19.9 Hz, replacing the singlet signal at δ 42.26.

2 : Solvent: ether, [**48**] = 128 mM, 1.1 equivalents *n*-Bu_3SnD, -78°C → R.T. Tri-*n*-butyltin deuteride (80 µl, 0.295 mmol, 1.1 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (120 mg, 0.256 mmol, 1.0 equivalent) in anhydrous ether (2.00 ml)

cooled to −78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (74 mg, 0.189 mmol, 74%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.90 H; δ 3.29, br. d, *J* 4.7 Hz, 0.10 H.

3 : Solvent : ether, [**48**] = 245 mM, 2 equivalents *n*-Bu_3SnD, -78°C → R.T. Tri-*n*-butyltin deuteride (133 µl, 0.491 mmol, 2.0 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (115 mg, 0.246 mmol, 1.0 equivalent) in anhydrous ether (1.00 ml) cooled to −78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (74 mg, 0.189 mmol, 74%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.95 H; δ 3.29, br. d, *J* 4.7 Hz, 0.05 H.

4 : Solvent : ether, [**48**] = 490 mM, 2 equivalents *n*-Bu_3SnD, -78°C → R.T. Tri-*n*-butyltin deuteride (85 µl, 0.314 mmol, 2.0 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (74 mg, 0.157 mmol, 1.0 equivalent) in anhydrous ether (320 µl) cooled to −78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (41 mg, 0.104 mmol, 60%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.94 H; δ 3.29, br. d, *J* 4.7 Hz, 0.06 H.

5 : Solvent : toluene, [48] = 245 mM, 2 equivalents *n*-Bu_3SnD, -78°C → R.T.

Tri-*n*-butyltin deuteride (60 µl, 0.220 mmol, 2.0 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (52 mg, 0.110 mmol, 1.0 equivalent) in anhydrous toluene (450 µl) cooled to –78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The toluene was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (15 mg, 0.039 mmol, 35%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.94 H; δ 3.29, br. d, *J* 4.7 Hz, 0.06 H.

6 : Solvent : ether, [48] = 92 mM, 1.1 equivalents *n*-Bu_3SnD, R.T.

Tri-*n*-butyltin deuteride (54 µl, 0.201 mmol, 1.1 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (86 mg, 0.183 mmol, 1.0 equivalent) in anhydrous ether (2.00 ml) at room temperature. The mixture was stirreed at room temperature for sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (42 mg, 0.108 mmol, 59%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.83 H; δ 3.29, br. d, *J* 4.7 Hz, 0.17 H.

7 : Solvent : ether, [48] = 245 mM, 2 equivalents *n*-Bu_3SnD, R.T.

Tri-*n*-butyltin deuteride (60 µl, 0.222 mmol, 2.0 equivalents) was added rapidly to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (52 mg, 0.111 mmol, 1.0 equivalent) in anhydrous ether (450 µl) at room temperature. The mixture was stirreed at room temperature for

sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (31 mg, 0.080 mmol, 72%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.90 H; δ 3.29, br. d, *J* 4.7 Hz, 0.10 H.

8 : Solvent : benzene, [**48**] = 245 mM, 2 equivalents *n*-Bu_3SnD, 80°C. Tri-*n*-butyltin deuteride (49 µl, 0.182 mmol, 2.0 equivalents) was added rapidly to a refluxing solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (86 mg, 0.183 mmol, 1.0 equivalent) in anhydrous benzene (370 µl). The mixture was refluxed for one hour. The benzene was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (14 mg, 0.037 mmol, 41%). ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**) except for : δ 3.05, d, *J* 5.4 Hz 0.69 H; δ 3.29, br. d, *J* 4.7 Hz, 0.31 H.

(S)-*deuterioglycine (132)*

(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiary-butoxycarbonyl)amino]-2-deuterioacetate (**128a**) (95 : 5 2-(*S*) : 2-(*R*) by ^{1}H-N.M.R. analysis) was dissolved in trifluoroacetic acid (0.5 ml) and the mixture left to stand at room temperature for ten minutes. 6N HCl (1 ml) was then added and the mixture refluxed for fifteen hours. After cooling to room temperature, water was added and the resultant solution washed with chloroform (2X). The aqueous layer was evaporated to dryness *in vacuo*. The residue was purified by ion exchange chromatography on Amberlite 1R-120 (H) to yield the *title compound* (6.0 mg, 0.079 mmol, 92%). M.P. 235-236°C; lit.[92] 234°C. M.S. 77 (21) 76 (M^+) (100) 75 (13). ^{1}H-N.M.R. (300 MHz, D_2O, internal reference 3-(trimethylsilyl)-1-propane-

sulphonic acid sodium salt) δ : 3.53, t, *J* 2 Hz. Lit.[13] (270 MHz, D_2O, no internal reference quoted) δ : 3.65, t.

(1S,4R)-ω-camphanoyl chloride (178)

Followed the method of Gerlach[93]. (1*S*,4*R*)-ω-camphanic acid monohydrate (99 mg) was converted to the *title compound* (81 mg, 82%). M.P. =69-71°C; lit.[93] 69-71°C.

methyl (1S,4R)-ω-camphanoylglycinate (129)

(*S*)-deuterioglycine (**132**) (3.8 mg, 50.0 μmol) was dissolved in methanol (5 ml) which had been treated with thionyl chloride (20 mg). After standing for sixteen hours, the methanol was evaporated *in vacuo*, and the residue dissolved in water (200 μl). Potassium bicarbonate (25.0 mg, 0.250 mmol), and ethyl acetate were then added. To the stirred mixture was added a solution of (1*S*,4*R*)-ω-camphanoyl chloride (**178**) (11.9 mg, 55.0μmol) in ethyl acetate (100 μl). Stirring was continued for a further two hours. The layers were then separated and the organic layer successively washed with dilute hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulphate and the ethyl acetate evaporated*in vacuo* to yield the *title compound* as a colourless oil which later solidified. Yield : 7.4 mg, 27.5 μmol, 55%). M.P. 80-82°C; lit[92] 84°C. ^{1}H-N.M.R. data consistent with that reported by Armarego *et al*[92]. ^{1}H-N.M.R. (300 MHz) δ: 0.98, s, 3H, (7' *gem.* CH_3); 1.11, s, 3H, (7' *gem.* CH_3); 1.12, s, 3H, (4' CH_3); 1.6-2.6, complex, 4H (5' and 6' CH_2); 3.77, s, 3H (CH_3O);

4.17, d, *J* 2.6 Hz, 0.08H (*pro-(R)* α-CH); 3.98, d, *J* 2.6 Hz, 0.92H (*pro-(S)* α-CH); 6.94, br. s, 1H (NH).

BROMINATION OF (*S*)-2-DEUTERIOGLYCINATE (128a), FOLLOWED BY REDUCTION WITH TRI-*n*-BUTYLTIN HYDRIDE

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiary-butoxycarbonyl)amino]-2-deuterioacetate (**128a**) (95 : 5 2-(*S*) : 2-(*R*) by ^{1}H-N.M.R. analysis) (18.1 mg, 46.3 μmol) was treated with *N*-bromosuccinimide (8.3 mg, 46.8 μmol) by the same procedure used for the undeuteriated compound (**48**). Tri-*n*-butyltin hydride (25 μl, 92.6 μmol, 2.0 equivalents) was added rapidly to a stirred solution of the intermediate bromide in anhydrous ether (500 μl) cooled to –78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (9.7 mg, 24.9 μmol, 54%). Mass spectroscopy indicated that the d_1:d_0 ratio was *ca.* 26 : 74, based on the relative intensities of the ions of m/z 391, 390 and 389. ^{1}H-N.M.R. (300 MHz) : identical to that of (**47**), except for the presence of a doublet at δ 3.29 (*J* 4.7 Hz) lying under the doublet of doublets centred at δ 3.29, which was detected by subtraction of the spectrum of (**47**).

N-*tertiarybutoxycarbonyl-2,2-dideuterioglycine (139)*

Following the method of Itoh *et al.*[38], 2,2-dideuterioglycine (400 mg, 5.19 mmol) was converted to the *title compound*.. Yield = 788 mg, 4.45 mmol, 86% ; m.p. = 75-76°C (cf. 77-78°C for the undeuterated

compound). ^{1}H-N.M.R. (300 MHz, d_6 D.M.S.O.) δ: 1.38, s, 9H (*t*-Boc CH_3); 7.06, s, 1H (N**H**); 10.61, br. s, 1H (CO_2**H**). Electron impact mass spectroscopy indicated that the d_2:d_1:d_0 ratio was *ca.* 96.9 : 2.5 : 0.6, based on the relative intensities of the molecular ions of m/z 177, 176 and 175 respectively.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]-2,2-dideuterioacetate (138)

N-tertiarybutoxycarbonyl-2,2-dideuterioglycine (**139**) (245 mg, 1.384 mmol) was esterified with (–)-8-phenylmenthol (296 mg, 1.272 mmol) using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil (434 mg, 1.108 mmol, 93%). Mass spectroscopy indicated that the d_2:d_1:d_0 ratio was *ca.* 91.6 : 8.4 : 0, based on the relative intensities of the molecular ions of m/z 392, 391 and 390. ^{1}H-N.M.R. (300 MHz) : identical to that of (**48**) except for the diminishment of the integrals of the two doublets of doublets centred at δ 3.05 and δ 3.29 from 1 H each to *ca.* 0.05 H and 0.03 H respectively. In addition, the amide proton resonated as a <u>singlet</u> at δ 4.33. Mass spectroscopy indicated that the d_2:d_1 ratio was *ca.* 92 : 8, based on the relative intensities of the ions of m/z 391, 390 and 389.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R)-2-[(tertiarybutoxycarbonyl)amino]-2-deuterioacetate (128b)

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiary-butoxycarbonyl)amino]-2,2-dideuterioacetate (**138**) (75 mg, 0.192 mmol) was treated with *N*-bromosuccinimide (34 mg, 0.192 mmol) in the same

manner as the undeuteriated compound (**48**). Tri-*n*-butyltin hydride (103 µl, 0.384 mmol, 2.0 equivalents) was added rapidly to a stirred solution of the uncharacterized bromide (**48b**) in anhydrous ether (740 µl) cooled to −78°C. The cold bath was left to equilibrate to room temperature over sixteen hours. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (49 mg, 0.127 mmol, 66%). Mass spectroscopy indicated that the d_1:d_0 ratio was *ca.* 94.6 : 5.4, based on the relative intensities of the ions of m/z 391, 390 and 389. ^{1}H-N.M.R. (300 MHz) : identical to that of (**48**) except for : δ 3.05, d, *J* 5.4 Hz 0.11 H; δ 3.29, br. d, *J* 4.7 Hz, 0.89 H.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (157)

1 : [**48**] = 66 mM, 80°C.

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (190 mg, 0.406 mmol, 66 mM), allyltri-*n*-butyltin (295 mg, 0.822 mmol) and azobisisobutyronitrile (*ca.* 3 mg) in anhydrous benzene (6.2 ml) was refluxed for five hours. Upon cooling to room temperature, the benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (133 mg, 0.309 mmol, 76%). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]pent-4-enoate (**79a**). H.P.L.C. analysis indicated that the ratio of the 2-(*S*):2-(*R*) allylglycinates (**79a**) and (**79b**) was 93:7.

2 : [48] = 288 mM, 80°C.

Treatment of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (67 mg, 0.144 mmol, 288 mM) with allyltri-*n*-butyltin (105 mg, 0.317 mmol, 2.2 equivalents) and azobisisobutyronitrile (*ca*. 1 mg) in anhydrous benzene (0.5 ml) as described above gave the *title compound* (48 mg, 0.112 mmol, 78%). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenyl-ethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (**79a**). H.P.L.C. analysis indicated that the ratio of the 2-(*S*):2-(*R*) allylglycinates (**79a**) and (**79b**) was 92:8.

3 : [48] = 66 mM, R.T.

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (77 mg, 0.164 mmol, 66 mM), allyltri-*n*-butyltin (120 mg, 0.361 mmol) and azobisisobutyronitrile (*ca*. 1 mg) in anhydrous benzene (6.2 ml) was left to stand at room temperature for sixteen hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (60 mg, 0.139 mmol, 85%). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-pent-4-enoate (**79a**). H.P.L.C. analysis indicated that the ratio of the 2-(*S*):2-(*R*) allylglycinates (**79a**) and (**79b**) was 96:4.

4 : [48] = 66 mM, 5°C.

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (53 mg, 0.113 mmol, 66 mM), allyltri-*n*-butyltin (82 mg, 0.248 mmol) and azobisisobutyronitrile (*ca.* 1 mg) in anhydrous benzene (1.7 ml) was left to stand at 5°C for sixteen days. Fresh A.I.B.N. was added every two days in *ca.* 1 mg portions. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (24 mg, 0.055 mmol, 49%). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]pent-4-enoate (**79a**). H.P.L.C. analysis indicated that the ratio of the 2-(*S*):2-(*R*) allylglycinates (**79a**) and (**79b**) was 94:6.

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-*methylcyclohexyl* (S)-2-*[(tertiarybutoxycarbonyl)amino]pentanoate (158a)*

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]pent-4-enoate (**157a**), a (1.5 mg, 3.5 µmol) was reduced over 10% Pd/C (0.7 mg) in methanol (1 ml) under one atmosphere of hydrogen for sixteen hours. The catalyst was removed by filtration through celite and the methanol evaporated to give the *title compound* (1.3 mg, 3.0 µmol, 87%) as a colourless oil. ^{1}H-N.M.R. : (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]pent-4-enoate (**79a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R)-2-*[(tertiarybutoxycarbonyl)amino]*pentanoate *(158b)*

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*)-2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (**157b**) (1.0 mg, 2.3 μmol) was reduced over 10% Pd/C (0.5 mg) in methanol (1 ml) by the same method used for the 2-(*S*)-norvalinate (**158a**) to give the *title compound* (0.8 mg, 1.8 μmol, 80%) as a colourless oil. ^{1}H-N.M.R. : (300 MHz) : identical to the spectrum of authentic (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*)-2-[(tertiarybutoxycarbonyl)amino]pentanoate (**79b**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl 2-*[(tertiarybutoxycarbonyl)amino]*pentanoate *(158)*

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*,*S*)-2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (**157**) (a 93 : 7 2-(*S*) : 2-(*R*) mixture of diastereomers, 15 mg, 36 μmol) was reduced over 10% Pd/C (7 mg) in methanol (1 ml) by the same method used for the 2-(*S*)-norvalinate (**158a**) to give the *title compound* (13 mg, 32 μmol, 88%) as a colourless oil. H.P.L.C. analysis indicated the presence of two components in a 93 : 7 ratio. The first-eluting component co-eluted with an authentic sample of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]pentanoate (**79a**), and the second-eluting component co-eluted with an authentic sample of the corresponding 2-(*R*) diastereomer (**79b**).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]-4-methylpent-4-enoate (159)

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (91 mg, 0.193 mmol), (2-methyl-2-propenyl)tri-*n*-butyltin (133 mg, 0.386 mmol) and azobisisobutyronitrile (*ca.* 1 mg) in anhydrous benzene (0.68 ml) was left to stand at room temperature for sixteen hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (69 mg, 0.156 mmol, 81%). H.P.L.C. analysis indicated the presence of two components in a 95 : 5 ratio. M.S. 443 (M^+), 387 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{42}NO_4$ ($[M + H]^+$) 444.311, found 444.313. Microanalysis: found C 72.70%, H 9.03%. $C_{27}H_{41}NO_4$ requires C 73.10%, H 9.32%. ^{1}H-N.M.R. (300 MHz) δ: 0.86, d, *J* 6.4 Hz, 3H (ring CH_3); 1.20, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.45, s, 9H (*t*Bu CH_3); 1.64, s, 3H, ($CH_3C=C$); 0.9-2.3, complex, 10H (methylene envelope); 3.77, m, 1H (α CH); 4.41, d, *J* 8.3 Hz, 1H (NH); 4.63, s, 1H (HCH=C); 4.75, s, 1H (HCH=C); 4.84, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.15-7.35, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.76 (CH_3CPh); 21.84 ($CH_3C=C$); 23.91 (CH_3CPh); 26.39 (ring CH_2CHCPh); 28.32 (*t*Bu CH_3); 28.96 (ring CH_3); 31.22 (ring $CHCH_3$); 34.52 (ring CH_2CHCH_3); 39.47, (CMe_2Ph); 40.44 ($CH_2C=C$); 41.37 (ring CH_2C-O); 50.22 (ring CHCPh); 51.68 (α CH); 75.72 (H-C-O); 79.21 (CMe_3); 113.89 ($CH_2=C$); 125.22, 125.30, 128.06, 154.99 (Ar); 140.95 ($C=CH_2$); 151.76 (*t*Boc C=O); 171.60 (ester C=O).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (R,S)-2-*[(tertiarybutoxycarbonyl)amino]*-4-methylpentanoate (161)

N-tertiarybutoxycarbonyl-(*R*,*S*)-leucine (**179**) was esterified with (−)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 87% yield. Microanalysis: found C 72.79%, H 9.63%. $C_{27}H_{43}NO_4$ requires C 72.77%, H 9.73%.

Small samples of the pure 2-(*S*) and 2-(*R*) diastereomers were obtained by preparative H.P.L.C:

Data for the 2-(*S*) diastereomer (**161a**): F.A.B. M.S. : m/z 446 ($[M + H]^+$), 390 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.80-0.95, complex, 9H (ring CH_3, δ CH_3's); 1.20 s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 1.1-2.1, complex, 11H (methylene envelope); 3.72, m, 1H (α CH); 4.26, d, *J* 8.9 Hz, 1H (NH); 4.78, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.10-7.35, complex, 5H (ArH).

Data for the 2-(*R*) diastereomer (**161b**): F.A.B. M.S. : m/z 446 ($[M + H]^+$), 390 ($[M + H]^+ - C_4H_8$). ^{1}H-N.M.R. (300 MHz) δ: 0.82-0.92, complex, 9H (ring CH_3, δ CH_3's); 1.23 s, 3H (CH_3CPh); 1.32, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.9-2.1, complex, 11H (methylene envelope); 3.97, m, 1H (α CH); 4.58, d, *J* 8.8 Hz, 1H (NH); 4.84, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.15-7.30, complex, 5H (ArH).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl (S)-2-*[(tertiarybutoxycarbonyl)amino]*-4-methylpentanoate *(161a)*

N-tertiarybutoxycarbonyl-(*S*)-leucine (**179a**) was esterified with (−)-8-phenylmenthol using the method of Hassner and Alexanian[45]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil in 73% yield. N.M.R. data : identical to the data quoted above for the 2-(*S*) diastereomer (**161a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl 2-*[(tertiarybutoxycarbonyl)amino]*-4-methylpentanoate *(160)*

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*,*S*)-2-[(tertiarybutoxycarbonyl)amino]-4-methylpent-4-enoate (**159**) (a 95 : 5 2-(*S*) : 2-(*R*) mixture of diastereomers, 20 mg, 46 μmol) was reduced over 10% Pd/C (10 mg) in methanol (1 ml) by the same method used for the 2-(*S*)-norvalinate (**158a**) to give the *title compound* (20 mg, 46 μmol, 100%) as a colourless oil. H.P.L.C. analysis indicated the presence of two components in a 94 : 6 ratio. The first-eluting component co-eluted with an authentic sample of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-4-methylpentanoate (**161a**), and the second-eluting component co-eluted with an authentic sample of the corresponding 2-(*R*) diastereomer (**161b**). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (**161a**).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-(tertiarybutoxycarbonyl)amino]-3-methylpent-4-enoate (162)

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (60 mg, 0.127 mmol), [(*E*)-(2-butenyl)]tri-*n*-butyltin (97 mg, 0.280 mmol) and azobisisobutyronitrile (*ca.* 1 mg) in anhydrous benzene (1.00 ml) was left to stand at room temperature for sixteen hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (47 mg, 0.105 mmol, 83%). M.S. 443 (M^+), 387 ($M^+ - C_4H_8$). Exact mass calculated for $C_{27}H_{42}NO_4$ ($[M + H]^+$) 444.311, found 444.309. ^{1}H-N.M.R. (300 MHz) δ: 0.75-0.95, complex, 6H (ring CH_3 and γ-CH_3); 1.22, s, 3H (CH_3CPh); 1.30, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.95-2.10, complex, 8H (methylene envelope); 2.36, complex, 1H (β-CH); 3.58, d of d, *J* 4.2, 8.6 Hz and 3.63, d of d, *J* 4.0, 8.7 Hz, total 1H (α CH); 4.70-5.05, complex, 4H (NH, H_2C=CH and HC-O); 5.40-5.70, complex, 1H (HC=CH_2); 7.15-7.35, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 14.90, 15.72 (γ-CH_3); 21.77 (CH_3CPh); 24.38, 24.25 (CH_3CPh); 26.41 (ring CH_2CHCPh); 28.29 (*t*Bu CH_3); 28.38, 28.49 (ring CH_3); 31.24 (ring $CHCH_3$); 34.46 (ring CH_2CHCH_3); 39.47, (CMe_2Ph); 39.67, 40.25 (CHC=C); 41.48, 41.53 (ring CH_2C-O); 50.48 (ring CHCPh); 56.90, 57.12 (α CH); 75.71, 75.79 (H-C-O); 79.33 (CMe_3); 115.40, 116.16, (CH_2=C); 125.28, 125.38, 127.95, 154.97 (Ar); 137.85, 138.80 (CH=CH_2); 151.23 (*t*Boc C=O); 170.78 (ester C=O).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (163)

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]-3-methylpent-4-enoate (**162**) (35 mg, 90 μmol) was reduced over platinum oxide (10 mg, 45μmol) in methanol (2 ml) by the same method used for the 2-(*S*)-norvalinate (**158a**) to give the *title compound* (33 mg, 84 μmol, 83%) as a colourless oil. H.P.L.C. analysis indicated the presence of three components in a 83 : 10.7 : 6.3 ratio. The first-eluting component co-eluted with authentic samples of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2*S*, 3*S*)-2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (**117a**) and the corresponding (2*S*, 3*R*) diastereomer (**117b**). The second-eluting component co-eluted with unreduced starting material (**162**). The third-eluting component co-eluted with an authentic sample of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (2*R*, 3*R*)-2-[(tertiarybutoxycarbonyl)amino]-3-methylpentanoate (**117c**). ^{1}H-N.M.R. (300 MHz) : comparison to the spectra of authentic (**117a**) and (**117b**) indicated that the (2*S*, 3*S*) : (2*S*, 3*R*) ratio was *ca.* 2 : 3.

triphenylprop-2-ynylstannane (150) and
triphenylprop-1,2-dienylstannane (170)

Followed the method of Le Quan and Cadiot[106]. (**150**) : 19% yield. M.P. : 80-82°C; lit[106] : 81-83°C. I.R. : 2110, 3290 cm^{-1}. (**170**) : 10% yield. M.P. : 58-60°C; lit[106] : 65°C. I.R. : 1926 cm^{-1}.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-3,4-dienoate (169)

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (79 mg, 0.168 mmol), triphenylprop-1,2-dienylstannane (**170**) (131 mg, 0.336 mmol) and azobisisobutyro-nitrile (*ca.* 1 mg) in anhydrous benzene (590 µl) was refluxed for five hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (38 mg, 0.090 mmol, 53%). H.P.L.C. analysis indicated the presence of two components in a 93 : 7 ratio. M.S. m/z 427 (M^+), 426 (M^+ - H), 371 (M^+ - C_4H_8). M.S. 427 (M^+), 371 (M^+ - C_4H_8). Exact mass calculated for $C_{26}H_{38}NO_4$ ($[M + H]^+$) 428.280, found 428.283. ^{1}H-N.M.R. (300 MHz) δ: 0.87, d, *J* 6.4 Hz, 3H (ring CH_3); 1.21, s, 3H (CH_3CPh); 1.31, s, 3H (CH_3CPh); 1.46, s, 9H (*t*Bu CH_3); 0.9-2.3, complex, 8H (methylene envelope); 4.09, m, 1H (α CH); 4.72, br. d, *J* 8.1 Hz, 1H (NH); 4.84, d of t, *J* 4.3, 10.7 Hz, 1H (HC-O); 4.90-5.15, complex, 3H (allenic CH); 7.10-7.35, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.76 (CH_3CPh); 23.99 (CH_3CPh); 26.40 (ring CH_2CHCPh); 28.32 (*t*Bu CH_3); 28.73 (ring CH_3); 31.26 (ring $CHCH_3$); 34.46 (ring CH_2CHCH_3); 39.53, (CMe_2Ph); 41.39 (ring CH_2C-O); 50.44 (ring CHCPh); 51.53 (α CH); 75.91 (H-C-O); 79.43 (CH_2=C=CH, CMe_3); 89.06 (CH=C=CH_2); 125.31, 128.04, 154.66 (Ar); 151.49 (*t*Boc C=O); 169.41 (ester C=O); 207.19 (CH_2=C=CH_2). I.R. ν 1958 cm^{-1}.

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl 2-*[(tertiarybutoxycarbonyl)amino]*pentanoate *(171)*

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*,*S*)-2-[(tertiarybutoxycarbonyl)amino]pent-3,4-enoate (**169**) (a 93 : 7 2-(*S*) : 2-(*R*) mixture of diastereomers, 11 mg, 27 μmol) was reduced over 10% Pd/C (5 mg) in methanol (1 ml) by the same method used for the 2-(*S*)-norvalinate (**157a**) to give the *title compound* (9 mg, 21 μmol, 78%) as a colourless oil. H.P.L.C. analysis indicated the presence of two components in a 93 : 7 ratio. The first-eluting component co-eluted with an authentic sample of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]pentanoate (**158a**), and the second-eluting component co-eluted with an authentic sample of the corresponding 2-(*R*) diastereomer (**158b**). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (**75a**).

(1R, 2S, 5R)-2-*(1-methyl-1-phenylethyl)*-5-methylcyclohexyl 2-*[(tertiarybutoxycarbonyl)amino]pent-4-ynoate (172)*

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (60 mg, 0.128 mmol), triphenylprop-2-ynylstannane (**150**) (100 mg, 0.256 mmol) and azobisisobutyro-nitrile (*ca.* 1 mg) in anhydrous benzene (450 μl) was left to stand at room temperature for sixteen hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give the *title compound* (32 mg, 0.074 mmol, 58%) as a colourless oil which became a white solid upon standing. H.P.L.C. analysis indicated the presence of two components in a 97 : 3 ratio. Recrystallization from

hexane gave white crystals, M.P. = 126-127°C. M.S. m/z 427 (M^+), 371 ($M^+ - C_4H_8$). Exact mass calculated for $C_{22}H_{29}NO_4$ ($M^+ - C_4H_8$) 371.210, found 371.212. Microanalysis: found C 73.26%, H 8.80%. $C_{26}H_{37}NO_4$ requires C 73.04%, H 8.72%. ^{1}H-N.M.R. (300 MHz) δ: 0.88, d, *J* 6.5 Hz, 3H (ring CH_3); 1.20, s, 3H (CH_3CPh); 1.29, s, 3H (CH_3CPh); 1.47, s, 9H (*t*Bu CH_3); 0.9-2.3, complex, 8H (methylene envelope); 2.08, br. s, 1H, (HC≡C); 2.12, d of d of d, *J* 16.9, 4.1, 2.5 Hz, 1H (HCHC≡CH); 2.41, d of d of d, *J* 16.9, 4.0, 2.8 Hz, 1H (HCHC≡CH); 3.59, d of t, *J* 7.8, 4.4 Hz, 1H (α CH); 4.83, d of t, *J* 4.3, 10.8 Hz, 1H (HC-O); 5.08, d, *J* 7.8 Hz, 1H (NH); 7.15-7.40, complex, 5H (ArH). ^{13}C-N.M.R. (75.5 MHz) δ: 21.76 (CH_3CPh); 22.37 (CH_2C≡C); 23.19 (CH_3CPh); 26.27 (ring CH_2CHCPh); 28.32 (*t*Bu CH_3); 29.28 (ring CH_3); 31.23 (ring $CHCH_3$); 34.50 (ring CH_2CHCH_3); 39.38, (CMe_2Ph); 41.18 (ring CH_2C-O); 50.44 (ring CHCPh); 51.65 (α CH); 70.91 (C≡CH); 75.91 (H-C-O); 79.03 (C≡CH); 79.69 (CMe_3); 125.24, 125.37, 127.98, 154.84 (Ar); 151.73 (*t*Boc C=O); 169.65 (ester C=O). I.R. ν 3300 cm^{-1}.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pentanoate (173)

(1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*R*,*S*)-2-[(tertiarybutoxycarbonyl)amino]pent-4-ynoate (**172**) (a 97 : 3 2-(*S*) : 2-(*R*) mixture of diastereomers, 22 mg, 52 μmol) was reduced over 10% Pd/C (10 mg) in methanol (1 ml) by the same method used for the 2-(*S*)-norvalinate (**158a**) to give the *title compound* (16 mg, 37 μmol, 71%) as a colourless oil. H.P.L.C. analysis indicated the presence of two components in a 97 : 3 ratio. The first-eluting component co-eluted with an authentic sample of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]pentanoate (**75a**), and the second-eluting

component co-eluted with an authentic sample of the corresponding 2-(*R*) diastereomer (75b). ^{1}H-N.M.R. (300 MHz) : identical to the spectrum of authentic (75a).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-4-ynoate (172) and
(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-3,4-dienoate (169)

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate (**48**) (82 mg, 0.176 mmol), triphenylprop-2-ynylstannane (**150**) (137 mg, 0.352 mmol) and azobisisobutyro-nitrile (*ca*. 1 mg) in anhydrous benzene (270 µl) was refluxed for five hours. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give a *ca*. 2:1 mixture of (**172**) and (**169**) respectively, as indicated by comparison of the ^{1}H-N.M.R. spectrum of the mixture with the spectra of pure (**172**) and (**169**). Total yield 34 mg, 0.079 mmol, 45%.

(S)-allylglycine (164)

(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiary-butoxycarbonyl)amino]pent-4-enoate (**157a**) (>99% 2-(*S*) by H.P.L.C. analysis) (283 mg, 0.659 mmol) was dissolved in trifluoroacetic acid (2 ml) and the mixture left to stand at room temperature for ten minutes. 6N HCl (4 ml) was then added and the mixture refluxed for fifteen hours. After cooling to room temperature, water was added and the resultant

solution washed with chloroform (2X). The aqueous layer was evaporated to dryness *in vacuo*. The residue was purified by ion exchange chromatography on Amberlite 1R-120 (H) to yield the *title compound* (49.6 mg, 0.428 mmol, 65%). M.S. 134 (By-product $[M + H]^+$, 18), 116 (allylglycine $[M + H]^+$, 100). ^{1}H-N.M.R. (300 MHz, D_2O) δ: 2.50, complex, 2H (β CH_2); 3.67, d of d, *J* 5.1, 6.8 Hz, 1H (α-CH); 5.13, d, *J* 8.0 Hz, 1H (HCH=CH); 5.14, d, *J* 18.0 Hz, 1H (HCH=CH); 5.60-5.75, complex, 1H (HCH=CH). This spectrum was identical to that of authentic (*R,S*)-allylglycine, except for the presence of an extraneous signal (δ 1.11, d, *J* 6.0 Hz, 0.17H). No distinct resonance complementary to this signal was discernable in the spectrum. $[\alpha]_D^{24} = -30.3°$, C=3.77, H_2O. Lit.[103]: –37.1°, C=4, H_2O.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (79)

(*S*)-allylglycine (**164**) (41 mg, 0.359 mmol) (derived from hydrolysis of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]pent-4-enoate (**157a**)) was converted to its *N*-*t*-Boc derivative (**73a**) by the method of Itoh *et al*[38]. Yield = 59 mg, 0.276 mmol, 77%. 48 mg (0.223 mmol) of (**73a**) was converted to the *title compound* by esterification with (–)-8-phenylmenthol (57 mg. 0.246 mmol) by the method of Hassner and Alexanian[45]. Yield = 85 mg, 0.198 mmol, 89%. H.P.L.C. analysis showed that the 2-(*S*) : 2-(*R*) ratio was 98.3 : 1.7).

REACTION OF BROMIDE (48) WITH ALLYLTRI-*n*-BUTYLTIN IN THE PRESECE OF HYDROQUINONE

A solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tertiarybutoxycarbonyl)amino]-2-bromoacetate **(48)** (41 mg, 87.3 μmol), allyltri-*n*-butyltin (58 mg, 175 μmol) and hydroquinone (2 mg, 17.4 μmol) in anhydrous benzene (1.3 ml) was left to stand at room temperature in the dark for sixteen hours. Monitoring of the reaction by T.L.C. revealed that the *title compound* had formed. H.P.L.C. analysis indicated that the ratio of the 2-(*S*):2-(*R*) allylglycinates **(157a)** and **(157b)** was 96:4.

1 Morrison, J.D. and Mosher, H.S., *Asymmetric Organic Reactions*, American Chemical Society, Washington, D.C. (**1976**).

2 Cram, D.J. and Elhafez, F.A.A., *J. Am. Chem. Soc.*, **1952**, *74*, 5828.

3 Birtwhistle, J.S., Morrison, J.D., Sanderson, W.A. and Mosher, H.S., *J. Org. Chem.*, **1964**, *29*, 37.

4 Morrison, J.D., Burnett, R.E., Aguiar, A.M., Morrow, C.J. and Phillips, C., *J. Am. Chem. Soc.*, **1971**, *93*, 1301.

5 Inch, T.D., Lewis, G.J., Sainsbury, G.L. and Sellers, D.J., *Tetrahedron Lett.*, **1969**, 3657.

6 Mellin, G.W. and Katzenstein, M., *New Engl. J. Med.* , **1962**, *267*, 1184.

7 von Blasche, G., Kraft, H.P., Firkentscher, K. and KÖhler, F., *Arzneim.-Forsch. / Drug Res.*, **1979**, *29*, 1640.

8 Itumi, Y., Chibatata, I. and Itoh, T., *Angew. Chem. Int. Ed. Engl.* , **1978**, *17*, 176.

9 Wagner, I. and Musso, H., *Angew. Chem. Int. Ed. Engl.*, **1983**, *22*, 816.

10 Mazur, R.H., Schlatter, J.M. and Goldkamp, A.H., *J. Am. Chem. Soc.*, **1969**, *91*, 2684.

11 Williams, R.M., Sinclair, P.J., Zhai, D. and Chen, D., *J. Am. Chem. Soc.*, **1988**, *110*, 1547.

12 Schollkopf, U. and Neubauer, H.-J., *Synthesis* , **1982**, 861.

13 Williams, R.M., Zhai, D. and Sinclair, P.J., *J. Org. Chem.*, **1986**, *51*, 5021.

14 Knowles, W.S., Sabacky, M.J., Vineyard, B.D. and Weinkauff, D.J., *J. Am. Chem. Soc.*, **1975**, *97*, 2567.

15 Duhamel, L. and Plaquevent, J., *J. Am. Chem. Soc.*, **1978**, *100*, 7415.

16 Becker, Y., Eisenstadt, A. and Stille, J.K., *J. Org. Chem.*, **1980**, *45*, 2145.

17 Evans, D.A., Britton, T.C., Dorow, R.L. and Dellaria, J.F., *Tetrahedron*, **1988**, *44*, 5525.

18 Oppolzer, W. and Moretti, R., *Tetrahedron*, **1988**, *44*, 5541.

19 Evans, D.A., Ellman, J.A. and Dorow, R.L., *Tetrahedron Lett.*, **1987**, *28*, 1128.

20 Oppolzer,W., Pedrosa, R. and Moretti, R., *Tetrahedron Lett.*, **1986**, *27*, 831.

21 Tabushi, I., Kuroda, Y., Yamada, M., Higashimura, H. and Breslow, R., *J. Am. Chem. Soc.*, **1985**, *107*, 5545.

22 Williams, R.M., *Synthesis of Optically Active α–Amino Acids*, Pergamon Press, Oxford, **1989**.

23 Whitesell, J.K., Bhattacharya, A. and Henke, K., *J. Chem. Soc., Chem. Commun.*, **1982**, 988.

24 Whitesell, J.K., *Acc. Chem. Res.*, **1985**, *18*, 280.

25 Whitesell, J.K., Younathan, J.N., Hurst, J.R. and Fox, M.A., *J. Org. Chem.*, **1985**, *50*, 5499.

26 Fiaud, J. and Kagan, B., *Tetrahedron Lett.*, **1971**, 1019.

27 Yamamoto, Y., Ito, W. and Maruyama, K., *J. Chem. Soc., Chem. Commun.*, **1985**, 1131.

28 Castelhano, A.L., Horne, S., Billedeau, R. and Krantz, A., *Tetrahedron Lett.*, **1986**, *27*, 2435.

29 Kober, R., Papadopoulos, K., Miltz, W., Enders, D. and Steglich, W., *Tetrahedron*, **1985**, *41*, 1693.

30 Lidert, Z. and Gronowitz, S., *Synthesis*, **1980**, 322.

31 Zhai, D., Zhai, D. and Williams, R.M., *J. Am. Chem. Soc.*, **1988**, *110*, 2501.

32 Sinclair, P.J., Zhai, D., Reibenspeis, J. and Williams, R.M., *J. Am. Chem. Soc.*, **1986**, *108*, 1103.

33 Williams, R.M., Sinclair, P.J., Zhai, D. and Chen, D., *J. Am. Chem. Soc.*, **1988**, *110*, 1547.

34 Zimmernann, J. and Seebach, D., *Helv. Chim. Acta*, **1987**, *70*, 1104.

35 Viehe, H.G., Merényi, R., Stella, L. and Janousek, Z., *Angew. Chem. Int. Ed. Engl.*, **1979**, *18*, 917.

36 Easton, C.J. and Hay, M.P., *J. Chem. Soc., Chem. Commun.*, **1986**, 55.

37 Castelhano, A.L., Horne, S., Taylor, G.J., Billedeau, R. and Krantz, A., *Tetrahedron*, **1988**, *44*, 5451.

38 Itoh, M., Hagiwara, D. and Kamiya, T., *Tetrahedron Lett.*, **1975**, 4393.

39 Bodanszky, M., Klausner, Y.S. and Ondetti, M.A., *Peptide Synthesis*, Wiley, New York, **1976**, 26.

40 Rando, R., *Nature* (London), **1974**, *250*, 586.

41 Scannel, J.P., Preuss, D.L., Demney, T.C., Sello, L.H., Williams, T. and Stempel, A., *J. Antibiot.*, **1972**, *25*, 122.

42 Afzali-Ardakani, A. and Rapoport, H., *J. Org. Chem.*, **1986**, *51*, 5021.

43 Barton, D.H.R., Crich, D., Herve, Y., Potier, P. and Thierry, J., *Tetrahedron*, **1985**, *41*, 4347.

44 Hanessian, S. and Sahoo, S.P., *Tetrahedron Lett.*, **1984**, *25*, 1425.

45 Hassner, A. and Alexanian, V., *Tetrahedron Lett.*, **1978**, 4475.

46 Corey, E.J. and Ensley, H.E., *J. Am. Chem. Soc.*, **1975**, *97*, 6908.

47 Ensley, H.E., Parnell, C.A. and Corey, E.J., *J. Org. Chem.*, **1978**, *43*, 1610.

48 Boeckmann, R.K., Naegely, P.C. and Arthur, S.D., *J. Org. Chem.*, **1980**, *45*, 752.

49 Helmchen, G. and Schmierer, R., *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 205.

50 Oppolzer, W. and LÖher, H.J., *Helv. Chim. Acta*, **1981**, *64*, 2802.

51 Oppolzer, W., Kurth, M., Reichlin, D. and Moffatt, F., *Tetrahedron Lett.*, **1981**, 2545.

52 Oppolzer, W. and LÖher, H.J., *Helv. Chim. Acta*, **1981**, *64*, 2808.

53 Whitesell, J.K., Bhattacharya, A., Aguilar, D.A. and Henke, K., *J. Chem. Soc., Chem. Commun.*, **1982**, 989.

54 Whitesell, J.K., Bhattacharya, A., Buchanan, C.M., Chen, H.H., Deyo, D., James, D., Liv, C.-L. and Minton, M.A., *Tetrahedron*, **1986**, *42*, 2993.

55 Oppolzer, W., Robbiani, C. and Bättig, K., *Helv. Chim. Acta*, **1980**, *63*, 2015.

56 Ort, O., *Organic Syntheses*, **1987**, *65*, 203.

57 Whitesell, J.K., Younathan, J.N., Hurst, J.R. and Fox, M.A., *J. Org. Chem.*, **1985**, *50*, 5499.

58 Whitesell, J.K., Lawrence, R.M. and Chen, H.-H., *J. Org. Chem.*, **1986**, *51*, 4779.

59 Dale, J.A. and Mosher, H.S., *J. Am. Chem. Soc.*, **1973**, *95*, 512.

60 Sullivan, G.R., *Top. Stereochem.*, **1978**, *10*, 287.

61 Pirkle, W.H. and House, D.W., *J. Org. Chem.*, **1979**, *44*, 1957.

62 Frank, H., Nicholson, G.J. and Bayer, E., *J. Chrom. Science*, **1977**, *15*, 174.

63 Hamon, D.P.G.H., *private communication*.

64 Burgess, V.A., *Ph.D. Thesis, The University of Adelaide*, **1989**.

65 Whitesell, J.K., *J. Org. Chem.*, **1986**, *51*, 551.

66 Harwood, L.M., *Aldrichimica Acta*, **1985**, *18*, 25.

67 Still, W.C., Kahn, M. and Mitra, A., *J. Org. Chem.*, **1978**, *43*, 2923.

68 Brown, D.W., *J. Chem. Edu.*,**1985**, *62*, 209.

69 Ashby, E.C. and Becker, W.E., *J. Am. Chem. Soc.*, **1963**, *85*, 118.

70 Ashby, E.C. and Smith, M.B., *J. Am. Chem. Soc.*, **1964**, *86*, 4363.

71 Prelog, V., *Helv. Chim. Acta*, **1953**, *36*, 308.

72 Prelog, V., *Bull. Soc. Chim. Fr.*, **1956**, 987.

73 Mathieson, A.McL., *Tet. Lett.*, **1965**, 4137.

74 Ermert, P., Meyer, J., Stucki, C., Schneebeli, J. and Obrecht, J.-P., *Tetrahedron Lett.*, **1988**, 1265.

75 Clough, G.W., *J. Chem. Soc.*, **1918**, *113*, 526.

76 Münster, P. and Steglich, W., *Synthesis*, **1987**, 223.

77 Yamamoto, Y. and Ito, W., *Tetrahedron*, **1988**, *44*, 5415.

78 Baker, K.V., Brown, J.M., Hughes, N., Skarnulis, A.J. and Sexton, A., *J. Org. Chem.*, **1991**, *56*, 698.

79 Easton, C.J., *Advances in Detailed Reaction Mechanisms*; Coxon, J.M., Ed.; J.A.I. Press: Greenwich, CT., **1991**; Vol. *1*, p. 83.

80 Beckwith, A.L.J., *Tetrahedron*, **1981**, *37*, 3073.

81 Verhoeven, J.W., *Recl. Trav. Chim. Pays-Bas*, **1980**, *99*, 143.

82 Giese, B., *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 969.

83 Hart, D.J. and Huang, H.C., *Tetrahedron Lett.*, **1985**, *26*, 3749.

84 Crich, D. and Davies, J.W., *Tetrahedron Lett.*, **1987**, *28*, 2205.

85 Easton, C.J., Scharfbillig, I.M. and Tan, E.W., *Tetrahedron Lett.*, **1988**, 1565.

86 Ramalingam, K., Nanjappan, P., Kalvin, D.M. and Woodard, R.W., *Tetrahedron*, **1988**, *44*, 5597 and references therein.

87 Kajiwara, M., Lee, S.F. and Scott, A.I., *J. Chem. Soc., Chem. Commun.*, **1978**, 967.

88 Retey, J. and Robinson, J.A., *Stereospecificity in Organic Chemistry and Enzymology*; Verlag Chemie: Weinheim, **1982**; Vol. 13, 161.

89 Kuivila, H.G. and Beumel, O.F., *J. Am. Chem. Soc.*, **1961**, *83*, 1246.

90 Ruchardt, C. and Beckhous, H.-D., *Topics in Current Chem.*, **1985**, *88*, 1.

91 Bordwell, F.G. and Harrelson, J.A., *Can. J. Chem.*, **1990**, *68*, 1714.

92 Armarego, W.L.F., Milloy, B.A. and Pendergast, W., *J. Chem. Soc., Perkin Trans. I*, **1976**, 2229.

93 Gerlach, H., *Helv. Chim. Acta*, **1968**, *51*, 1587.

94 Beckwith, A.L.J. and Brumby, S., *J. Chem. Soc., Perkin Trans. II*, **1987**, 1801.

95 Slet, V., *Tezisy Dokl.-Resp. Konf. Molodykh Uch.-Khim.*, 2nd **1977**, *2*, 53 (*Chem. Abstr.*, **1980**, *93*, 132764).

96 Slet, V., Salandi, H., Lumiste, T. and Arro, I., *Eesti NSV Tead-Akad. Toim., Fuus., Mat.*, **1976**, *25*, 46 (*Chem. Abstr.*, **1976**, *85*, 160486).

97 Guindon, Y., Yoakim, C., Lemieux, R., Boisvert, L., Delorme, D. and Lavallée, J.-F., *Tetrahedron Lett.*, **1990**, 2845.

98 Easton, C.J. and Scharfbillig, I.M., *J. Org. Chem.*, **1990**, *55*, 384.

99 Baldwin, J.E., Adlington, R.M., Lowe, C., O'Neil, I.A., Sanders, G.L., Schofield, C.J. and Sweeney, J.B., *J. Chem. Soc., Chem. Commun.*, **1988**, 1030.

100 Walsh, C., *Tetrahedron*, **1982**, 871.

101 Baldwin, J.E., Adlington, R.M. and Basak, A., *J. Chem. Soc., Chem. Commun.*, **1984**, 1284.

102 Castelhano, A.L., Pliura, D.H., Taylor, G.J., Hsieh, K.C. and Krantz, A., *J. Am. Chem. Soc.*, **1984**, *106*, 2734.

103 Black, S. and Wright, N.G., *J. Biol. Chem.*, **1955**, *213*, 39.

104 Curran, D.P., Shen, W., Zhang, J. and Heffner, T.A., *J. Am. Chem. Soc.*, **1990**, *112*, 6738.

105 Guindon, Y., Lavallée, J.-F., Boisvert, L., Chabot, C., Delorme, D., Yoakim, C., Hall, D., Lemieux, R. and Simoneau, B., *Tetrahedron Lett.*, **1991**, 27.

106 Le Quan, M. and Cadiot, P., *C. R. Acad. Sci., Ser. C.*, **1962**, *254*, 133.

107 Baldwin, J.E., Adlington, R.M., Birch, D.J., Crawford, J.A. and Sweeney, J.B., *J. Chem. Soc., Chem. Commun.*, **1986**, 1339.

108 Petrov, A.A. and Fedorova, A.V., *Russ. Chem. Rev.*, *33*, 1, and references therein.

109 Abeles, R.H. and Walsh, C.T., *J. Am. Chem. Soc.*, **1973**, *95*, 6124.

110 Washtien, W. and Abeles, R.H., *Biochemistry*, **1977**, *16*, 2485.

111 Walker, G., *New Scientist*, **1991**, *130, no. 1767*, 17.

112 Max, J., *Annalen*, 1909, 369, 276.