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The Asymmetric Synthesis of α-Amino Acids *via* the Addition of Grignard Reagents to Imine Derivatives.

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Abstract: The ester 8-phenylmenthyl *N*-Boc-glycinate **5a**, undergoes free radical bromination by *N*-bromosuccinimide to give 8-phenylmenthyl *N*-Boc-bromoglycinate **8**. Treatment of the bromide **8** with a variety of Grignard reagents at low temperature gave 8-phenylmenthyl (*S*)-*N*-Boc-2-alkylglycinates with high diastereoselectivity. Conditions were found for the hydrolysis of these derivatives with no racemization of the resultant amino acid.

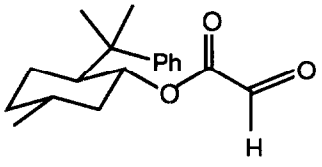
As well as the twenty common α-amino acids, there exist hundreds of other non-proteinogenic amino acids[1]. Many of these are biologically active and the unique biological action usually resides in one enantiomer. Although the twenty common amino acids can be readily obtained from natural sources[2], this is not necessarily true for the rarer analogues and in many cases asymmetric synthesis may well be the best method to obtain quantities of them. Even though a large number of ways to prepare such compounds exists[3], the importance of enantiomerically pure amino acids and the diverse range of structures found, means there is still a need to develop new ways to prepare such compounds in optically active form.

The asymmetric synthesis of α-amino acids described in this paper was devised after a report[4] that high asymmetric induction is found in the reaction of the glyoxylate ester **1** with Grignard reagents. The obvious relationship of imines such as **2** to the glyoxylate **1**, gave rise to speculation that similar levels of asymmetric induction might be discovered in the reaction of such imines with Grignard reagents and that this could lead to an asymmetric synthesis of amino acids. Similar earlier work[5], in which menthol was used as the chiral auxiliary, did indeed give some optically active amino acid derivatives, albeit with modest diastereomeric excess (d.e.). However, most Grignard reagents used in that earlier work underwent preferential conjugate addition at the nitrogen atom rather than at the imine carbon. Later work has shown that competitive addition at all three sites can occur[6].

It seemed likely that the presence of an acyl group on the imino nitrogen of such imine derivatives would reduce or eliminate attack by Grignard reagents at the nitrogen. This idea was supported by a report[7] in which C-alkylation of acyliminoacetates by enamines led to the asymmetric synthesis of amino acids. A paper[8] describing the synthesis of racemic α-alkenyl amino acids by the addition of two equivalents of Grignard reagent to the α-chloroglycine derivative **3** set the stage for the work reported here. The free radical bromination of a glycine

derivative appeared to be a more convenient method of introducing an α–halogen than had been used to make compound **3**. As a consequence of this the *t*-butoxycarbonyl (Boc) group was chosen as the acyl group to be on nitrogen since it should be inert to bromination and yet be readily removable at a later stage. A synthesis of racemic amino acids employing this approach appeared[9] soon after the work reported here had been started.

After the ideas developed above had been clearly demonstrated, in these laboratories, but before the work was suitable for publication, a preliminary report[10] of a similar approach appeared. However, we present here the full details of our work, alluded to earlier[11,12], which include a method for the hydrolysis of the optically active intermediates to the α-amino acids without racemisation. In the earlier report[10] this important step was not achieved.



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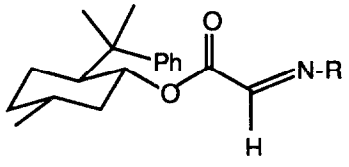

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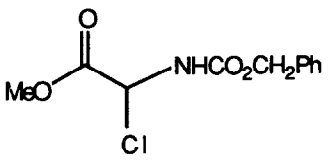

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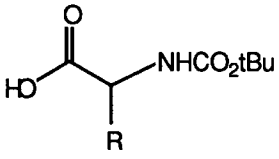
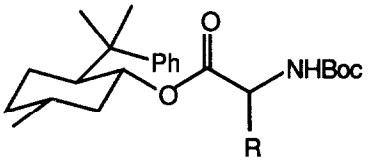


4 a) R = H, b) R = Me, c) R = nPr
d) R = iPr, e) R = Ph, f) R = CH_2Ph
g) R = Et, h) R = $CH_2CH{=}CH_2$



5 a) R = H, b) R = Me, c) R = nPr
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g) R = Et, h) R = $CH_2CH{=}CH_2$
i) R = $CH{=}CH_2$

Results and Discussion.

Asymmetric syntheses.

Esterification of N-Boc derivative of glycine **4a** with (-)-8-phenylmenthol by the use[13] of dicyclohexylcarbodiimide (DCC) and *N,N*-dimethylaminopyridine (DMAP) gave as an oil, in 93% yield, the glycine derivative **5a**. Both ^1H and ^{13}C NMR analysis of ester **5a** unambiguously confirmed the expected structure. Of particular interest were the signals due to the two diastereotopic α-protons which appeared as the AB part of an ABX system at 300 MHz. One doublet of doublets was at δ 3.05 (J 15.1, 5.9 Hz) and the other at δ 3.29 (J 15.1, 5.3 Hz). The amide proton signal was a broadened doublet of doublets centred at δ 4.38. The broad-band decoupled ^{13}C NMR spectrum of this compound exhibited the expected nineteen signals. A combination of DEPT experiments and the use of ^{13}C NMR correlation tables, enabled the unambiguous

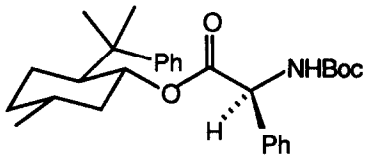
assignment of every resonance. This proved to be of great benefit in the interpretation of the ^{13}C NMR spectra of all of the α-substituted derivatives reported herein.

Since this was an exploratory project, the decision was made to study the synthesis of mainly common or known amino acids for which the standard derivatives of known stereochemistry could be made from available optically active or racemic amino acids.

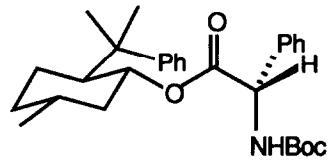
The synthesis of the known *N*-Boc protected amino acids **4b-4h** by the use[14] of 2-*t*-butyloxycarbonyloxyimino-2-phenylacetonitrile (BOC-ON) was both straightforward and high yielding (66-84%). The crude *N*-Boc amino acids produced were pure enough to esterify directly with (−)-8-phenylmenthol, by the use[13] of DCC and DMAP. The derivatives were then obtained analytically pure, in 76-96% yield, after purification by chromatography. All of the diastereomeric pairs **5b- 5h** (*R* and *S* at C2) were resolved by TLC. This observation was important because it meant that products derived from the asymmetric Grignard additions could be purified by column chromatography and, the diastereomerically pure samples thus obtained, should then yield enantiomerically pure amino acids, regardless of the selectivity of the asymmetric step. Analysis by HPLC of the diastereomeric pairs **5b- 5h** (*R* and *S* at C2) showed that, in all cases, the two diastereomers separated to baseline resolution, under the same conditions and this presented a very simple, rapid and sensitive analytical method which allowed the Grignard addition products to be analyzed directly.

A small sample of each diastereomer within each epimeric pair was obtained by preparative HPLC. FAB mass spectroscopic analysis of these diastereomerically pure samples confirmed that, in each case, the two components within each mixture of diastereomers possessed the same, and expected, molecular weight. In all cases, the NMR spectra were consistent with the expected structures and, for each diastereomeric pair, the 2-(*S*) and 2-(*R*) diastereomers were clearly differentiated. The ^1H NMR spectrum of 8-phenylmenthyl (*R*)-*N*-Boc-phenylglycinate **5e** (R at C2) revealed an interesting and unusual feature of this molecule. The two diastereotopic geminal methyl groups of the 8-phenylmenthyl moiety resonated at unexpectedly high field (δ 0.80 and 1.00) when compared to those (δ1.23-1.25 and 1.31-1.33) of the other 2-(*R*) epimers in this series. Furthermore the chemical shift difference between these two signals of 0.20 ppm for derivative **5e** (R at C2) is substantially larger than the typical value of 0.08-0.10 ppm found in the other derivatives. 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 **5e** (S at C2) , whose geminal methyl groups have chemical shifts of δ 1.22 and 1.32. This strongly infers that the α-phenyl group, in the 2-(*S*) diastereomer points away from, whereas in the 2-(*R*) diastereomer it points towards, the phenyl group of the chiral auxiliary. These effects can best be rationalized by the assumption that the amino acid moiety in each diastereomer adopts the *Z* conformation **6Z** and **7Z** respectively. If the *E* rotamer predominated in each (**6E** or **7E**), 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 probable that all of the 8-phenylmenthyl esters **5** of the *N*-Boc-amino acids adopt the *Z* conformation.

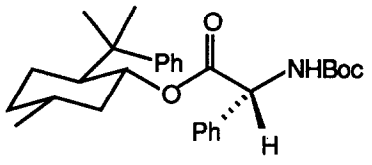
The bromination of 8-phenylmenthyl *N*-Boc-glycinate **5a** with freshly recrystallized *N*-bromosuccinimide under ultraviolet light in dry carbon tetrachloride, at reflux, proceeded rapidly to afford the bromide **8** as a colourless oil, in virtually quantitative yield. The high purity of the product was indicated by the ^1H NMR spectrum, which showed the complete absence of the α-proton signals of the starting material and the appearance



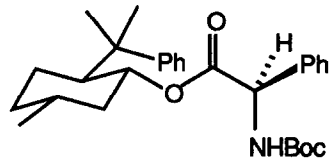
6Z



6E



7Z

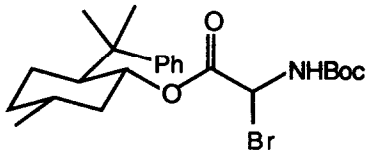


7E

of a doublet at δ 4.88 attributed to the α-proton of the product **8**. Care needed to be exercised in handling this bromide as it was labile and sensitive to moisture. Generally, it 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.

A very interesting result concerning this α-bromo ester is that it is almost certainly obtained as one diastereomer. This conclusion is based, in part, on the 300 MHz ^{1}H NMR spectrum of bromide **8**. Only one resonance for each type of proton is seen. This is convincing evidence in light of the ^{1}H NMR spectra of the diastereomeric mixtures **5b-5h**, which exhibited dual resonances for many of the protons. The bromide **9** was produced by bromination of menthyl *N*-Boc-glycinate**10** and it clearly showed an approximately 1:1 mixture of diastereomers in its ^{1}H NMR spectrum. The observation, that the bromide **8** appeared to be mainly one diastereomer, has led to the development of some interesting radical chemistry[11,12] the details of which will be published elsewhere.

It was found that the imine **11**, the expected intermediate from the addition of the Grignard reagent to the bromide **8**, could be generated by treatment of **8** in anhydrous ether with one equivalent of triethylamine. The imine **12** of the menthyl analogue was produced from bromide **9** in a similar manner. The imines **11** and **12** were insufficiently stable for full characterization, but the ^{1}H NMR spectral data of the two compounds were consistent with the structures. Some interesting observations can be made from the spectral data which are listed in **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 **11** and **12** can readily adopt conformations in which the α-carbon atom of these 8-phenylmenthyl imino esters is situated over the face of the phenyl ring. 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 shielding. A similar effect was reported[15] for the aldehydic proton of a series of glyoxylates (e.g **1**) formed from chiral auxiliaries related to and including 8-phenylmenthol. In that study it was shown that there was a rough correlation between the amount of shielding observed for that proton and the efficiency of the chiral auxiliary in diastereoselective reactions.



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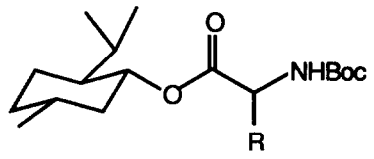
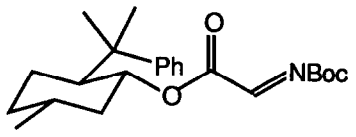


9 R = Br

10 R = H



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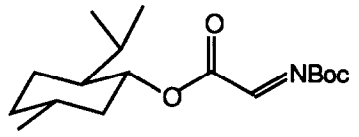

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Table 1

Auxiliary	α Proton Chemical Shift (δ)		
	PARENT (No.)	BROMIDE (No)	IMINE (No.)
Menthol	3.89 (10)	6.22 (9)	7.73 (11)
8-Ph-Menthol	3.17 (5)	4.88 (8)	6.70 (10)

Except for the experiments involving vinylmagnesium bromide, the Grignard reagents used in the alkylation studies described here were synthesized from the appropriate alkyl halide in ether and standardized. The Grignard reagent (2.2 equivalents) was added to an ethereal solution of the bromide **8**, at –78°C, the mixture was stirred at –78°C for 2 h., allowed to warm to room temperature and then quenched with an excess of saturated ammonium chloride solution. Chromatographic purification was necessary in all cases in order to remove low R_f impurities but care was taken to avoid fractionation of the two diastereomers produced. By this procedure, the products were obtained in the widely varying yields of 51-84% (**Table 2**) but the poorer yields could not be improved. For each product, TLC, ^1H and ^{13}C NMR analysis indicated that exclusive C-alkylation had occurred. Furthermore, comparison with the corresponding standard diastereomeric pair, described above, revealed that, in most cases, mainly one diastereomer had been formed, indicating that high asymmetric induction had occurred in the Grignard reaction. Compounds **5h** (entry 7) and **5i** (entry 8, no standards available) however, showed some signs of a second diastereomer by both TLC and ^1H NMR analysis. It was necessary to use HPLC analysis for an accurate, quantitative determination of the diastereomeric excess (d.e.) values. Analysis of the Grignard adducts by HPLC was straightforward in all cases except for entries 4 and 5. These samples were contaminated by minor impurities which had very similar retention times to the minor, 2-(*R*) diastereomers, and this prevented accurate integration of the peaks due to those diastereomers. Thus, the values for the d.e. of these samples are nominally 90%, since ^1H- and ^{13}C NMR did not show the minor, 2-(*R*) diastereomer and it would have been detected at the 5% level.

Table 2

Entry	R	No.	Yield (%)	D. E. (%)
1	Me	5(b)	72	98 [a]
2	*n*-Pr	5(c)	84	95
3	*i*-Pr	5(d)	51	98 [a]
4	Ph	5(e)	82	90 [b]
5	CH_2Ph	5(f)	58	90 [b]
6	Et	5(g)	82	95
7	$CH_2CH{=}CH_2$	5(h)	67	57
8	$CH{=}CH_2$	5(i)	52	51

All reactions in diethyl ether at -78°C except for entry 7 (THF, -20°C).

a) 2-(*R*) diastereomer not detected by HPLC

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

The chemical and optical yields for the Grignard addition reactions, presented in **Table 2,** show that most of these reactions proceed with high diastereoselectivity and in acceptable yield. The major diastereomers shown in entries 1, 2 and 3 correlated with the authentic 8-phenylmenthyl esters of (*S*)-*N*-Boc-alanine, (*S*)-*N*-Boc-norvaline, and (*S*)-*N*-Boc-valine **5b**, **5c** and **5d** (all *S* at C2). This confirms that the major diastereomers produced in these Grignard addition reactions have the (*S*) configuration at the α-carbon. In all three cases, the 2-(*S*) diastereomer was the first-eluting isomer. In addition, in each case, the α-proton of the 2-(*S*) diastereomer resonated at substantially higher field than the α-proton of its 2-(*R*) counterpart (**Table 3**). This observation can be rationalized[15] in terms of the preferred *Z* conformations **13** and **14** for the two diastereomers. In the *(S)* diastereomer, the α-proton spends more time in the shielding region of the phenyl ring.

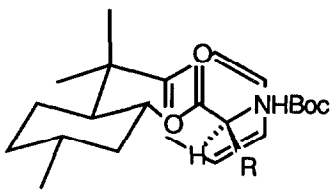
Table 3

Entry	R	No.	$\delta_{\alpha-H}$ (ppm)		Δδ (ppm)
			2-(*S*)	2-(*R*)	
1	Me	5(b)	3.65	3.96	0.31
2	*n*-Pr	5(c)	3.64	3.97	0.37
3	*i*-Pr	5(d)	3.53	4.07	0.54
4	Ph	5(e)	4.34	5.13	0.79
5	CH_2Ph	5(f)	3.87	4.04	0.17
6	Et	5(g)	3.57	3.93	0.36
7	$CH_2CH{=}CH_2$	5(h)	3.64	3.98	0.34
8	$CH{=}CH_2$	5(i)	4.07	4.54	0.47

The C2 configuration of the major diastereomer produced in the remaining Grignard addition reactions was not confirmed by direct correlation with the corresponding authentic 2-(*S*) derivatives. However, in all cases the major diastereomer eluted first and the chemical shift of its α-proton was lower than that of the minor diastereomer (**Table 3**). This provides strong evidence for the *(S)* configuration of these compounds.

The need to change the solvent to THF in the reaction of the bromide **8** with vinylmagnesium bromide was due to the irreproducibly poor yields obtained when the reaction was run in ether, probably due to solubility problems. Spectroscopic data clearly established that the two compounds produced in THF were the diastereomers **5i**, and that conjugation had not occurred. The major diastereomer was the first eluting on HPLC and the α-proton of this diastereomer resonated further upfield than that of the epimer. The two diastereomers were separated by preparative HPLC and each of them was separately hydrogenated and compared with the diastereomeric *N*-Boc-2-aminobutanoates **5g**. The major unsaturated diastereomer **5i** correlated with the major saturated diastereomer **5g**. Clearly, the major unsaturated diastereomer **5i** has the *(S)* configuration also.

An explanation for the formation of predominantly the *(S)* configuration in these reactions can be given in terms of the rationalisation presented earlier[4] for the reactions of the glyoxylate **1**. The presumption is made that the imine **11** is behaving analogously to the glyoxylate ester **1**. That is, the ester carbonyl and imino group are held *syn* by magnesium ion, as shown in **15**. The selective formation of the 2-(*S*) isomers, upon addition of Grignard reagents to the bromide, then comes about by attack from the less-hindered *Si* face which is opposite to the phenyl group.



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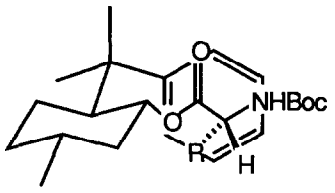

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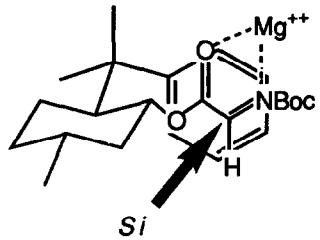

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The reason for the reduced stereoselectivity in the cases of the vinylglycine **5i** and allylglycine **5h** syntheses is not known but may be due to the different extents of aggregation of these Grignard reagents. It was suggested[4] that the aggregation of methyllithium profoundly influenced the diastereoselectivity of its addition reaction with 8-phenylmenthyl glyoxylate **1**. Alkylmagnesium bromides are known to be aggregates in ether[16], whereas they are monomeric in THF solution[17]. The reduced effective size of the incoming nucleophile, when the Grignard reagent is not aggregated, may account for the poorer facial selectivity towards the imino group. The allylmagnesium bromide reaction was, however, conducted in ether where aggregation would be expected. Since this Grignard reagent may react through the 1 or 3 position[18], perhaps it is also effectively less aggregated.

After the completion of this work, the asymmetric synthesis of some vinylglycine derivatives, *via* alkynylglycine derivatives, was reported[19].

A Method for the Hydrolysis of the Amino Acid Derivatives.

In the previous report[10] of similar work, hydrolysis of the amino acid derivatives without racemisation was not achieved, therefore, the task of developing such a hydrolysis procedure was undertaken. No conditions were given for the attempts made in the earlier work[10] but it was assumed that the standard procedure for the hydrolysis of amino acid derivatives was tried. It was considered that the most probable way that these compounds differed from normal amino acid esters and amides is that they may not be soluble in the aqueous medium employed. The prior removal of the *N*-Boc protecting group with trifluoroacetic acid (TFA) should give salts which are more likely to be soluble in the aqueous medium. The model compound chosen to test this hypothesis was 8-phenylmenthyl (*S*)-*N*-Boc-alaninate **5b** (*S* at C2), prepared from enantiomerically pure (*S*)-alanine and shown to be diastereomerically pure by HPLC analysis. Accordingly, the ester **5b** was treated with TFA but the isolated TFA salt was found to be insoluble in 6 mol dm^{-3} HCl. It was, in fact, soluble in a 19:1 hexane/chloroform mixture and this indicates the degree of hydrophobicity the ester group imposes. However, if the salt was not isolated but left instead in the TFA and to this was added the 6 mol dm^{-3} HCl solution, then hydrolysis could be effected. The revised procedure involved treatment of the ester **5b** (*ca.* 100mg) with TFA (1 mL) for fifteen minutes, followed by the addition of 6 mol dm^{-3} HCl (2 mL) and refluxing the homogeneous solution for fifteen hours. The alanine was isolated by ion exchange chromatography on Amberlite 1R-120 (H) and it had, within experimental error, the same optical rotation as the starting alanine. The hydrolysate was converted to methyl (*S*)-*N*-benzoylalaninate by treatment with methanolic hydrogen chloride to give methyl (*S*)-alaninate hydrochloride which was then treated with benzoyl chloride under Schotten-Baumann conditions. The corresponding racemic alanine derivative was resolvable into two enantiomers on an optically active HPLC column[21]. Under the same conditions, the product derived from the hydrolysis showed, to the limits of detection, none of the *(R)* derivative confirming that no racemisation had occurred throughout this whole procedure. This procedure was also used successfully with other derivatives [11,12].

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. ^1H NMR and ^{13}C NMR spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer in $CDCl_3$ with TMS as internal standard. TLC was performed on Merck DC-Alufolien Kiselgel 60 F_{254} Art. 5554. and developed using a solution of 10% w/v ammonium molybdate in 1M HCl followed by heating. Flash Chromatography[21] was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Dry column chromatography[22] was performed on Merck Kieselgel 60 HF_{254} Art. 7739. HPLC chromatography was carried out on 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. FAB mass spectra were recorded with a Vacuum

Generators ZAB 2HF mass spectrometer with argon gas and a glycerol matrix. Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl.

Synthesis of the standard amino acid derivatives 5(a-h).

The known *N*-Boc amino acids were synthesized[14] from the corresponding amino acids, esterified[13] with (-)-8-phenylmenthol[24] and purified by flash chromatography to give the derivatives:

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (tert-butoxycarbonyl)aminoacetate (5a) 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%. ^1H NMR (300 MHz) δ: 0.87, d, *J* 6.6 Hz, 3H (ring **CH3**); 1.18, s, 3H (**CH3**CPh); 1.29, s, 3H (**CH3**CPh); 1.43, s, 9H (*t*Bu **CH3**); 0.8-2.1, complex, (methylene envelope); 3.05, dd, *J* 5.9, 15.1 Hz, 1H (*pro-R* α-**CH**); 3.29, dd, *J* 5.3, 15.1 Hz, 1H (*pro-S* α **CH**); 4.38, br. m, 1H (**NH**); 4.87, dt, *J* 4.2, 10.7 Hz, 1H (**HC**-O); 7.1-7.4, complex, 5H (**ArH**). ^{13}C NMR (75.5 MHz) δ: 21.64 (**CH3**CPh); 22.66 (**CH3**CPh); 26.15 (ring **CH2**CHCPh); 28.22 (*t*Bu **CH3**); 29.45 (ring **CH3**); 31.13 (ring **CH**CH3); 34.37 (ring **CH2**CHCH3); 39.28, (**CMe2**Ph); 41.49 (ring **CH2**C-O); 42.26 (α **CH2**); 50.15 (ring **CH**CPh); 74.73 (H-**C**-O); 79.27 (**CMe3**); 125.07,125.20, 127.79, 155.34 (Ar); 151.73 (*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-[(tert-butoxycarbonyl)amino]propanoate (5b) 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: 2-(*S*) diastereomer : FAB M.S. : m/z 404 ($[M + H]^+$), 348 ($[M + H]^+$ - C_4H_8). ^1H NMR (300 MHz) δ: 0.87, d, *J* 6.2 Hz, 3H (ring **CH3**); 1.09, d, *J* 7.1 Hz, 3H (α **CH3**); 1.20, s, 3H (**CH3**CPh); 1.30, s, 3H (**CH3**CPh); 1.46, s, 9H (*t*Bu **CH3**); 0.8-2.1, complex, (methylene envelope); 3.65, m, 1H (α **CH**); 4.49, d, *J* 7.2 Hz, 1H (**NH**); 4.81, dt, *J* 4.3, 10.7 Hz, 1H (**HC**-O); 7.1-7.4, complex, 5H (**ArH**). ^{13}C NMR (75.5 MHz) δ: 18.44, (α **CH3**); 21.75 (**CH3**CPh); 23.88 (**CH3**CPh); 26.47 (ring **CH2**CHCPh); 28.41 (*t*Bu **CH3**); 28.93 (ring **CH3**); 31.26 (ring **CH**CH3); 34.56 (ring **CH2**CHCH3); 39.54, (**CMe2**Ph); 41.41 (ring **CH2**C-O); 49.12 (α **CH**); 50.34 (ring **CH**CPh); 75.32 (H-**C**-O); 79.28 (**CMe3**); 125.31,128.05, 154.83 (Ar); 151.7 (*Boc* **C**=O); 172.18 (ester **C**=O). 2-(*R*) diastereomer: FAB M.S. : m/z 404 ($[M + H]^+$), 348 ($[M + H]^+$ - C_4H_8). ^1H-N.M.R (300 MHz) δ: 0.86, d, *J* 6.4 Hz, 3H (ring **CH3**); 1.20, d, *J* 7.1 Hz, 3H (α **CH3**); 1.23, s, 3H (**CH3**CPh); 1.32, s, 3H (**CH3**CPh); 1.44, s, 9H (*t*Bu **CH3**); 0.8-2.1, complex, (methylene envelope); 3.96, m, 1H (α **CH**); 4.78, d, *J* 8.1 Hz, 1H (**NH**); 4.87, dt, *J* 4.4, 10.7 Hz, 1H (**HC**-O); 7.1-7.4, complex, 5H (**ArH**). ^{13}C NMR (75.5 MHz) δ: 18.00, (α **CH3**); 21.71 (**CH3**CPh); 26.15 (ring **CH2**CHCPh); 26.99 (**CH3**CPh); 27.62 (ring **CH3**); 28.35 (*t*Bu **CH3**); 31.32 (ring **CH**CH3); 34.50 (ring **CH2**CHCH3); 40.06, (**CMe2**Ph); 41.67 (ring **CH2**C-O); 49.84 (α **CH**); 50.08 (ring **CH**CPh); 76.16 (H-**C**-O); 79.10 (**CMe3**); 125.33, 125.52, 128.00, 154.84 (Ar); 150.96 (*Boc* **C**=O); 172.18 (ester **C**=O).

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (S)-2-[(tert-butoxycarbonyl)amino]propanoate (5b) was also obtained from pure (*S*)-alanine. The data were the same as those of the first eluting diastereomer above.

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tert-butoxycarbonyl)amino]pentanoate (5c) 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: 2-(*S*) diastereomer: FAB M.S. : m/z 432 ($[M + H]^+$), 376 ($[M + H]^+$ - C_4H_8). ^1H NMR (300 MHz) δ: 0.80-0.95, complex, 6H (ring **CH3** and δ **CH3**); 1.21, s, 3H (**CH3**CPh); 1.30, s, 3H (**CH3**CPh); 1.46, s, 9H (*t*Bu **CH3**); 0.95-1.90, complex, (methylene envelope); 2.05, dt, *J* 3.2, 8.9 Hz, 1H

(ring CH); 3.64, br. dd, *J* 5.7, 13.8 Hz, 1H (α CH); 4.52, d, *J* 8.7 Hz, 1H (NH); 4.79, dt, *J* 4.3, 10.8 Hz, 1H (HC-O); 7.15-7.35, complex, 5H (ArH). ^{13}C NMR (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 (*Boc* C=O); 171.92 (ester C=O). 2-(*R*) diastereomer: FAB M.S. : m/z 432 ([M + H]$^+$), 376 ([M + H]$^+$ - C_4H_8). ^{1}H NMR (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, (methylene envelope); 3.97, br. dd, *J* 8.2, 12.8 Hz, 1H (α CH); 4.72, d, *J* 9.3 Hz, 1H (NH); 4.85, dt, *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-[(tert-butoxycarbonyl)amino]pentanoate (5c) was also obtained from pure (*S*)-norvaline. The data were the same as those of the first eluting diastereomer above.

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate (5d) 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: 2-(*S*) diastereomer: FAB 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, (methylene envelope); 3.53, dd, *J* 3.6, 8.6 Hz, 1H (α CH); 4.78, dt, *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 NMR (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 (*Boc* C=O); 171.46 (ester C=O). 2-(*R*) diastereomer: FAB M.S. : m/z 432 ([M + H]$^+$), 376 ([M + H]$^+$ - C_4H_8). ^{1}H NMR (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, (methylene envelope); 4.07, dd, *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 NMR (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 (*Boc* C=O); 171.07 (ester C=O).

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate (5d) was also obtained from pure (*S*)-valine. The data were the same as those for the first eluting diastereomer above.

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetate (5e) 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: 2-(*S*) diastereomer: FAB M.S. : m/z 466 ([M + H]$^+$), 410 ([M + H]$^+$ - C_4H_8). ^{1}H NMR (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, dt, *J* 2.8, 11.6 Hz, 1H (ring CH); 0.8-1.9, complex, (methylene envelope); 4.34, d, *J* 7.1 Hz, 1H (α CH); 4.79, dt, *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 NMR (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 (CMe_3); 125.28, 126.75, 127.92, 128.23, 137.41, 154.32 (Ar); 151.29 (*Boc* C=O); 169.98 (ester C=O). 2-(*R*) diastereomer: FAB M.S. : m/z 466 ($[M + H]^+$), 410 ($[M + H]^+ - C_4H_8$). ^1H NMR (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, (methylene envelope); 1.82, dt, *J* 3.3, 11.9 Hz, 1H (ring CH); 4.79, dt, *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 NMR (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 (*Boc* C=O); 169.42 (ester C=O).

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate (5f) 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: 2-(*S*) diastereomer: FAB M.S. : m/z 480 ($[M + H]^+$), 424 ($[M + H]^+ - C_4H_8$). ^1H NMR (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, (methylene envelope); 2.05, dt, *J* 3.5 *J* 11.2 Hz, 1H (ring CH); 2.62, dd, *J* 6.4 *J* 13.9 Hz, 1H (β CH); 2.87, dd, *J* 5.8 *J* 13.9 Hz, 1H (β CH); 3.87, dd, *J* 6.2, 14.3 Hz, 1H (α CH); 4.54, d, *J* 8.3 Hz, 1H (NH); 4.74, dt, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.0-7.4, complex, 10H (ArH). ^{13}C NMR (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 (*Boc* C=O); 170.91 (ester C=O). 2-(*R*) diastereomer: FAB M.S. : m/z 480 ($[M + H]^+$), 424 ($[M + H]^+ - C_4H_8$). ^1H NMR (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, (methylene envelope); 2.84, dd, *J* 7.5, 13.8 Hz, 1H (β CH); 2.98, dd, *J* 5.3, 13.8 Hz, 1H (β CH); 4.04, br. dd, *J* 7.5, 13.2 Hz, 1H (α CH); 4.56, d, *J* 7.1 Hz, 1H (NH); 4.84, dt, *J* 4.4, 10.7 Hz, 1H (HC-O); 7.0-7.4, complex, 10H (ArH). ^{13}C NMR (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 (*Boc* C=O); 170.30 (ester C=O).

(1R,2S,5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (R,S)-2-[(tert-butoxycarbonyl)amino]butanoate (5g) 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: 2-(*S*) diastereomer: FAB M.S. : m/z 418 ($[M + H]^+$), 362 ($[M + H]^+ - C_4H_8$). ^1H NMR (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, (methylene envelope); 3.57, br. dd, *J* 7.0, 13.3 Hz, 1H

(α CH); 4.63, d, *J* 7.7 Hz, 1H (NH); 4.80, dt, *J* 4.3, 10.7 Hz, 1H (HC-O); 7.10-7.30, complex, 5H (ArH). ^{13}C NMR (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 (*Boc* C=O); 171.67 (ester C=O). 2-(*R*) diastereomer: FAB M.S. : m/z 418 ($[M + H]^+$), 362 ($[M + H]^+ - C_4H_8$). ^{1}H NMR (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, (methylene envelope); 3.93, br. dd, *J* 7.4, 12.6 Hz, 1H (α CH); 4.76, d, *J* 8.1 Hz, 1H (NH); 4.86, dt, *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-[(tert-butoxycarbonyl)amino]pent-4-enoate (5h) 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: 2-(S) diastereomer: FAB M.S. : m/z 430 ($[M + H]^+$), 374 ($[M + H]^+ - C_4H_8$). ^{1}H NMR (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 (tBu CH_3); 0.8-2.4, complex, (methylene envelope); 3.64, br. dd, J 6.1, 13.2 Hz, 1H (α CH); 4.66, d, J 7.7 Hz, 1H (NH); 4.81, dt, 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 NMR (75.5 MHz) δ: 21.73 (CH_3CPh); 23.82 (CH_3CPh); 26.31 (ring CH_2CHCPh); 28.29 (tBu 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 (Boc C=O); 170.98 (ester C=O). 2-(R) diastereomer: FAB M.S. : m/z 430 ($[M + H]^+$), 374 ($[M + H]^+ - C_4H_8$). ^{1}H NMR (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 (tBu CH_3); 0.8-2.4, complex, 10H (methylene envelope); 3.98, br. dd, J 7.5, 12.5 Hz, 1H (α CH); 4.71, d, J 8.3 Hz, 1H (NH); 4.86, dt, 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[(tert-butoxycarbonyl)amino]bromoacetate (8) A suspension of *N*-bromosuccinimide (56mg, 0.314 mmol) in a refluxing solution of the ester 5a (121mg, 0.311 mmol) in dry carbon tetrachloride (5mL) was irradiated for 10 min 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 and then filtered. The solvent 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 NMR and ^{13}C NMR only. ^{1}H NMR (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, (methylene envelope); 4.82, dt, *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 NMR (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 (*Boc* C=O);164.60 (ester C=O).

(1R,2S,5R)-2-(1-methylethyl)-5-methylcyclohexyl (S)-2-[(tert-butoxycarbonyl)amino]acetate (10). *N*-tert-butoxycarbonylglycine was esterified[13] with (−)-menthol. 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 NMR (300 MHz) δ: 0.75, d, *J* 7.0 Hz, 3H (ring **CH**$_3$); 0.89, d, *J* 6.9 Hz, 3H (**CH**$_3$CPh); 0.91, d, *J* 6.6 Hz, 3H (**CH**$_3$CPh); 1.45, s, 9H (*t*Bu **CH**$_3$); 0.8-2.2, complex, (methylene envelope); 3.89, d, *J* 5.4 Hz, 2H (α-**CH**$_2$); 4.75, dt, *J* 4.4, 10.9 Hz, 1H (**HC**-O); 5.03, br. m, 1H (**NH**).

(1R, 2S, 5R)-2-(1-methylethyl)-5-methylcyclohexyl [(tert-butoxycarbonyl)amino]bromoacetate (9).This compound was prepared in a similar manner to bromo ester **8** above, in 91% yield. Due to the instability of this compound, characterization was possible by ^{1}H NMR only. ^{1}H NMR (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, (methylene envelope); 4.67, 4.73, each dt, *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 [(tert-butoxycarbonyl)iminoacetate (12). To a stirred solution of bromo derivative **9** (116 mg, 0.297 mmol) in anhydrous ether cooled to 0°C was added triethylamine (41 μL, 0.297 mmol). A white precipitate formed immediately. Stirring was continued for 1 min at 0°C and a further 10 min 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 NMR only. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.60-1.13, complex, 9H (ring **CH**$_3$, *gem.* **CH**$_3$); 1.53, s, 9H (*t*Bu **CH**$_3$); 1.13-2.30, complex, (methylene envelope); 4.67, dt, *J* 4, 10 Hz, 1H (**HC**-O); 6.17, br. s, 1H (α **CH**).

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl [(tert-butoxycarbonyl)iminoacetate (11). Following the procedure used for **12**, bromo derivative **8** (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, 73%). Due to the instability of this compound, characterization was possible by ^{1}H NMR only. ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.90, d, *J* 5 Hz, 3H (ring **CH**$_3$); 1.23 s, 3H (**CH**$_3$CPh); 1.32, s, 3H (**CH**$_3$CPh); 1.55, s, 9H (*t*Bu **CH**$_3$); 0.85-2.30, complex, (methylene envelope); 4.95, dt, *J* 4, 10 Hz, 1H (**HC**-O); 6.68, br. s, 1H (α **CH**); 6.90-7.30, complex, 5H (Ar**H**).

Grignard Reactions in Ether. These reactions were usually run in the same way. The Grignard reagent in ether (ca. 0.3-0.5 mmol, 2.2 equivs., 0.8-1.3M) was added dropwise, over a period of 0.5 h, to a stirred solution of bromoglycine derivative **8** (0.14- 0.23 mmol) in anhydrous ether (2.5-4.3 mL) cooled to -78°C under N_2, and then stirred for a further 2 h at -78°C before the cooling bath was removed. The reaction was quenched at room temp. by the addition of an excess of saturated NH_4Cl solution, extracted with ether which was then washed with water (x2), dried ($MgSO_4$) and the solvent removed. Chromatography on silica, taking care not to fractionate the diastereomers, gave the derivatives as recorded.

Methylmagnesium iodide gave 45 mg (0.112 mmol, 72%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]propanoate **5b**. HPLC analysis showed only one diastereomer which coeluted with the authentic 2-(*S*) diastereomer of **5b**.

n-Propylmagnesium bromide gave 54 mg (0.125 mmol, 84%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5- methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]pentanoate **5c**. HPLC analysis showed two diastereomers in a 97.5 : 2.5 ratio. The

major, first-eluting diastereomer coeluted with the authentic 2-(*S*) diastereomer of **5c** and the minor, second-eluting diastereomer coeluted with the authentic 2-(*R*) diastereomer of **5c**.

Isopropylmagnesium iodide gave 40 mg (0.093 mmol, 51%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5- methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate **5d**. HPLC analysis showed only one diastereomer which coeluted with the authentic 2-(*S*) diastereomer of **5c**.

Phenylmagnesium bromide gave 100 mg (0.213 mmol, 82%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*) [(tert-butoxycarbonyl)amino]phenylacetate **5e** and it coeluted on HPLC with an authentic sample of the (*S*) diastereomer of **5e**.

Benzylmagnesium bromide gave 55 mg (0.111 mmol, 58%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]-3-phenyl-propanoate **5f** and it coeluted on HPLC with an authentic sample of the (*S*) diastereomer of **5f**.

Ethylmagnesium bromide gave 53 mg (0.122 mmol, 82%). ^{1}H NMR and ^{13}C NMR showed resonances only for (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5- methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]butanoate **5g**. HPLC analysis showed two diastereomers in a 97.5 : 2.5 ratio. The major, first-eluting diastereomer coeluted with the authentic 2-(*S*) diastereomer of **5g** and the minor, second-eluting component coeluted with the authentic 2-(*R*) diastereomer of **5g**.

Allylmagnesium bromide gave 45 mg (0.104 mmol, 67%). ^{1}H NMR and ^{13}C NMR indicated that a mixture of the 2-(*S*) and 2-(*R*) diastereomers of (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tert-butoxycarbonyl)amino]pent-4- enoates **5h** had been formed. HPLC analysis showed two diastereomers in a 78.5 : 21.5 ratio. The major, first-eluting diastereomer coeluted with the authentic 2-(*S*) diastereomer of **5h** and the minor, second-eluting component coeluted with the authentic 2-(*R*) diastereomer of **5h**.

(1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tert-butoxycarbonyl)amino]but-3-enoate **5i**

Vinylmagnesium bromide (430 μL, 1.00 M in THF (Aldrich), 0.431 mmol, 2.2 equivalents) was added dropwise, over a period of 30 min, to a stirred solution of (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*) [(tert-butoxycarbonyl)amino]bromoacetate **8** (85 mg, 0.181 mmol, one equivalent) in anhydrous THF (3.5 mL) cooled to −20°C. The reaction mixture was stirred for a further 2 h at −20°C. The cold bath was then removed and the reaction mixture allowed to warm to room temperature, followed by workup as for the other Grignard reactions. Chromatography on silica gave the *title compound* in 52% yield. HPLC analysis showed two fractions in a 76.5:25.5 ratio. Small samples of each fraction were isolated by preparative HPLC : the major, first-eluting fraction showed: 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 NMR (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, (methylene envelope); 4.07, br. m, 1H (α CH); 4.70, d, *J* 7.8 Hz, 1H (NH); 4.83, dt, *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, ddd, *J* 5.0, 10.4, 17.1 Hz, 1H (CH=CH_2); 7.10-7.30, complex, 5H (ArH). ^{13}C NMR (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 (*Boc*

C=O); 169.62 (ester C=O). The minor, second-eluting fraction showed: 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 NMR (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, (methylene envelope); 4.54, br. m, 1H (α CH); 4.86, dt, *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, ddd, *J* 5.7, 10.3, 17.4 Hz, 1H (HCH=CH); 7.10-7.30, complex, 5H (ArH).

Reduction of diastereomers **5i** to the diastereomers **5g** The mixture of diastereomers **5i** (49 mg) was reduced over 10% Pd/C (35 mg) in methanol (5 mL) under one atmosphere of hydrogen for 16 h. Filtration of the mixture and removal of the solvent gave the saturated compound **5g** (44 mg, 88%) Comparison of the ^{1}H NMR spectra of this and the authentic diastereomers of **5g** indicated that a *ca.* 75 : 25 mixture of these two compounds was present and this was confirmed by HPLC analysis and co-elution with the authentic 2-(*S*) and 2-(*R*) (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tert-butoxycarbonyl)amino]butanoates **5g**.

Methyl (R,S)-N-benzoylalaninate methyl. 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 16 h. 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 2 h. 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, 91%. m.p. = 80-82°C. (Lit.[25] 80.5-81.5°C.) ^{1}H NMR (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).

Methyl (S)-N-benzoyl-(S)-alaninate. Synthesized by the method used above. Yield = 89%. ^{1}H NMR data identical to those obtained above.

Hydrolysis without racemisation of the amino acid derivative **5b**

(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methylcyclohexyl (*S*)-2-[(tert-butoxycarbonyl)amino]propanoate **5b** (239 mg, 0.592 mmol) was dissolved in TFA (1 mL) and the solution was left to stand for 15 min. 6 mol dm^{-3} HCl (2 mL) was then added, and the homogeneous solution was refluxed for 15 h. 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 92 mg (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) to give (*S*)-alanine (38 mg, 0.427 mmol, 72%), m.p. 293-294°C (dec.); (lit.[20] 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), and $[\alpha]^{24}$ = +16.1°(C=3, 1 mol dm^{-3} HCl). (Lit[20].: +14.7°(C=5.8, 1 mol dm^{-3} HCl)). The original (*S*)-alanine had $[\alpha]^{24}$ = +16.4°, (C=3, 1 mol dm^{-3} HCl). The free (*S*)-alanine (19 mg, 0.212 mmol) was derivatized by the method used above to yield the (*S*) ester (43 mg, 97%) with a ^{1}H NMR spectrum identical to that of authentic ester. Chiral HPLC analysis (Regis covalent Pirkle *N*-(3,5-dinitrobenzoyl)-(R)-phenylglycine derivatized column,[21] 25 cm x 4.6 mm, light petroleum/2-propanol, 9:1) showed only one enantiomer which coeluted with the authentic *(S)* enantiomer. Under the same conditions the racemic derivative resolved cleanly into two peaks.

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