Pergamon

Tetrahedron Vol. 51, No. 14, pp. 4183-4194, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00134-4

Asymmetric Induction in Acyclic Radical Reactions: Enantioselective Syntheses of α-Amino Acids *via* Carbon-Carbon Bond Forming Radical Reactions.

David P.G. Hamon*, Ralph A. Massy-Westropp and Pasquale Razzino

Chemistry Department, University of Adelaide, S.A. 5005, AUSTRALIA.

Abstract: The derivative of glycine, 8-phenylmenthyl *N*-Boc-2-bromoglycinate **1** reacted with allyltri-*n*-butylstannanes *via* the corresponding radical **2** by the S_H2' mechanism to give (2*S*) allyl amino acid derivatives with high diastereoselectivity. The reaction of **1** with triphenyl(1,2-propadienyl)stannane and triphenyl(2-propynyl)stannane gave the (2*S*) allenyl and (2*S*) propargyl amino acid derivatives respectively also with high diastereoselectivity but by a different mechanism.

INTRODUCTION

Recently we described[1] the enantioselective synthesis of (*S*)-2-deuterioglycine by free radical replacement of bromine by deuterium in the stannane reduction of the 2-bromoglycinate **1.** Having observed that the α-centred radical **2** undergoes highly stereoselective reduction with tri-*n*-butyldeuteriostannane, it was envisaged that this radical might also undergo diastereoselective carbon-carbon bond forming reactions with allyltri-*n*-butylstannanes[2] or with triphenyl(2-propynyl)stannane[3]. The radical chain "allyl transfer" reaction of allylstannanes has been used for the synthesis of γ,δ–amino acids concurrently but independently by Baldwin[4] and Easton[5]. The asymmetric synthesis of γ,δ–unsaturated amino acids[6,7] is 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[8].

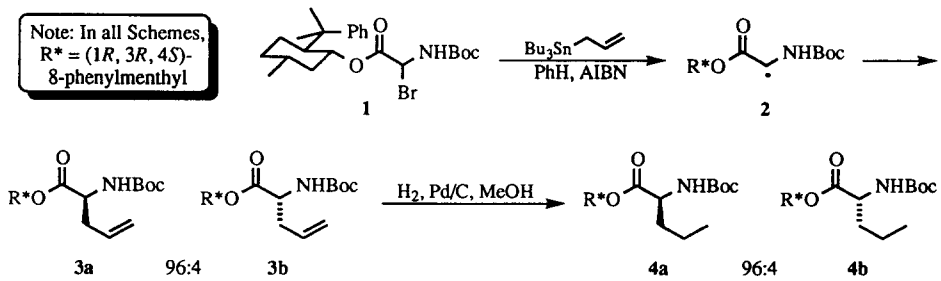
We present here the experimental details for a preliminary communication[9] which reported that the acyclic radical **2** undergoes highly diastereoselective carbon-carbon bond forming reactions[10] to give amino acid derivatives.

RESULTS AND DISCUSSION

Allyl Transfer Reactions

The conditions reported[5] for the allyl transfer reaction of allyltri-*n*-butylstannane with methyl *N*-benzoyl-2-bromoglycinate were employed in the analogous reaction with 8-phenylmenthyl *N*-Boc-2-bromoglycinate **1**. This involved treatment of the bromide **1** with two equivalents of allyltri-*n*-butylstannane[11] and 2 mole% of AIBN in dry benzene at reflux for five hours. Under these conditions, allyl transfer to the bromide **1** occurred giving, in 76% yield as a 93:7 mixture of diastereoisomers, the allylglycine derivatives **3a** and **3b**[12], which were isolated by preparative HPLC. Their ^{1}H NMR spectra were found to be identical to the fully characterised, authentic compounds derived from (*R,S*)-allylglycine[12].

Catalytic hydrogenation of the two separated diastereoisomers gave the saturated compounds **4a** and **4b**[12]. The ^{1}H NMR spectrum of the saturated derivative **4a** derived from the major isomer **3a** was identical to that of authentic 8-phenylmenthyl (2*S*)-*N*-Boc-norvalinate synthesised from (*S*)-norvaline[12] and the spectrum of the other saturated derivative was identical to that of the corresponding (*R*)-norvaline derivative. This established that the allyl transfer reaction favours production of the (2*S*) diastereoisomer.



Scheme 1

Both the major 8-phenylmenthyl *N*-Boc-allylglycinate diastereoisomer from the allyl transfer reaction and the major 8-phenylmenthyl *N*-Boc-2-deuterioglycinate from the corresponding deuteriation reaction[1] possessed the (2*S*) configuration. This was not unexpected as both products result from approach of a radicalophile to the same α-centred radical **2**, 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 rationalise the stereochemical course of the deuteriation reaction may be used for the analogous homolytic allylation reaction. That is, the capto-dative radical **2** adopts the geometry shown (**Scheme 1**) and is selectively attacked at the *si* face by the approaching allyltri-*n*-butylstannane.

Table 1. The Effect of Temperature and Concentration on the Reaction of Bromide 1 With Allyltri-*n*-butylstannane.

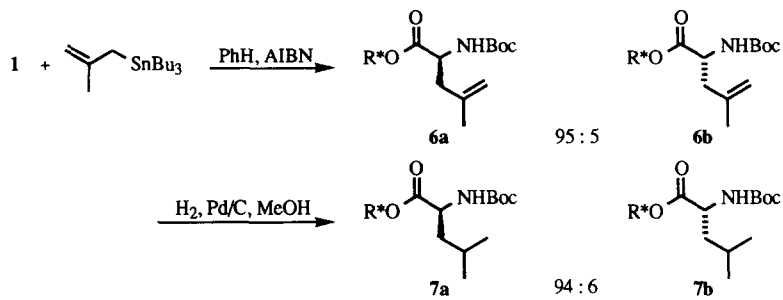
ENTRY	CONC. (1) (mM)	TEMP. (°C)	YIELD (3) (%)	D.E. (3) (%)
1	66	80	76	86
2	288	80	78	84
3	66	20	85	92
4	66	5	49	88

The level of diastereoselectivity in the reduction of the bromide **1** with tri-*n*-butyldeuteriostannane was found to vary with reaction temperature and concentration[1]. Hence, the effect of these two factors on the diastereoselectivity of the allylation reaction of the bromide was also investigated. The results of this study are summarised in **Table 1**. It transpired that the diastereoselectivity of the allyl transfer reaction was essentially independent of the concentration of the reactants, in marked contrast with the deuteriation reaction, where a change in concentration had a more marked effect on the diastereoselectivity. The diastereoselectivity of the allyl transfer reaction did improve somewhat (96:4) when the reaction was carried out at 20°C (Entry **3**) and the chemical yield also improved. In an attempt to increase the diastereoselectivity the reaction was run at 5°C (Entry **4**). However, the reaction was very slow at this temperature and even after

16 days the isolated yield of allylated compound was less than 50% and the diastereoselectivity had not improved.

A sample of (2*S*)-allylglycinate **3a** was obtained by chromatography and established to be >99% diastereoisomerically pure by HPLC analysis. Following the procedure, which had been developed by us previously[12], the ester was hydrolysed to yield allylglycine **5** with $[\alpha]_D^{24} = -30.3°$ (C=3.77, H_2O). Based on the reported[13] specific rotation for allylglycine ($[\alpha]_D^{24} = -37.1°$ (C=4, H_2O)), it appeared that the allylglycine obtained by hydrolysis may have partly racemised or may have been impure. Conversion of the amino acid back to the 8-phenylmenthyl ester derivatives **3** was considered to be the most expedient method to ascertain whether or not racemisation had occurred during hydrolysis, since HPLC conditions for the separation of the (2*S*) and (2*R*) 8-phenylmenthyl *N*-Boc-allylglycinates **3a** and **3b** were already established. Therefore the hydrolysis product was converted to the *N*-Boc derivative and this was esterified with 8-phenylmenthol. Analysis of the esterification product by HPLC revealed **3a** along with 1.5-1.8% of the corresponding **3b**. Thus hydrolysis had caused a maximum of 1.8% racemisation of the allylglycine.

The impurity in the allylglycine obtained by acid-catalysed hydrolysis may well be 4-hydroxynorvaline[14], formed by hydration of the double bond. A methyl group doublet resonance at δ 1.11 in the ^1H NMR spectrum of the crude amino acid mixture is consistent with the reported chemical shift for this compound[14] and an ion of m/z 134 (the molecular weight of protonated 4-hydroxynorvaline), present in the mass spectrum of the hydrolysate sample, further supports this. Although the hydrolysis procedure produced a chemically impure sample of allylglycine, the allylglycine itself was of high optical purity. Recrystallization should therefore provide a sample of both high chemical and optical purity.

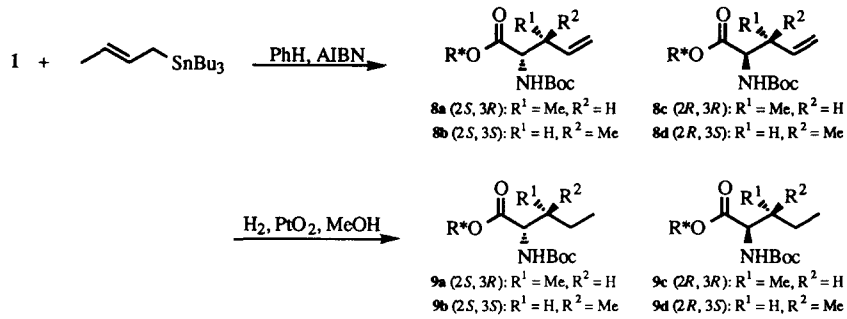


Scheme 2

The reaction of the bromide **1** with tri-*n*-butyl(2-methyl-2-propenyl)stannane[11] also proceeded with high diastereoselectivity (**Scheme 2**). The (2*S*) to (2*R*) ratio of the products **6a** and **6b** was 95:5. ^1H NMR, ^{13}C NMR and MS, along with microanalytical data, confirmed that transfer of the methallyl unit had taken place. Hydrogenation of the 95:5 mixture of diastereoisomers gave the leucine derivatives **7a** and **7b**. HPLC analysis revealed two components in a 94:6 ratio whose retention times correlated with those of the authentic **7a** and **7b**. These standards were obtained by preparative HPLC separation of the fully characterised diastereoisomeric pair obtained by the esterification of (*R,S*)-*N*-Boc-leucine with 8-phenylmenthol. The major saturated diastereoisomer was confirmed as the (2*S*) isomer by HPLC and ^1H NMR comparison with **7a** synthesised from (*S*)-leucine. In this way, the (2*R*) diastereoisomer **6b**, although not isolated and characterised, was shown to be the minor component of the allyl transfer reaction product.

The reaction of the bromide **1** with (*E*)-(2-butenyl)tri-*n*-butylstannane[15] represents an important

extension of the methodology just developed. The reaction between the α-centred radical **2** and the butenyl allylstannane involves the formation of two chiral centres due to the coupling of the *si* diastereoface of the radical and an enantioface of the olefin. This reaction, therefore, has the potential to give rise to the four diastereoisomers shown in **Scheme 3**. The highly diastereoselective reaction of the bromide with allylstannanes 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 **8c** and **8d** would be formed in only minor amounts. For high asymmetric induction to be achieved at the β-centre of the resultant γ,δ-unsaturated α-amino acid derivative, one of the enantiotopic faces of the 2-butenyl moiety of the stannane must preferentially approach the α-centred radical.



Scheme 3

The bromide **1** was treated with (*E*)-(2-butenyl)tri-*n*-butylstannane under the optimum conditions already established. HPLC analysis of the product **8** (obtained in 83% yield) suggested that this material was essentially homogeneous with respect to the C-2 stereochemistry, as mainly one peak was evident and the C-2 epimers of all *N*-Boc-α-amino acid 8-phenylmenthyl esters we had prepared previously were quite well resolved by HPLC. However, the amount of selectivity at C-3 was impossible to gauge by HPLC as it was unknown whether the (2*S*, 3*S*) and (2*S*, 3*R*) diastereoisomers were resolvable. NMR spectroscopy also was not useful for the determination of the isomer ratios because, although both the ^{1}H and ^{13}C NMR spectra clearly indicated a mixture of what appeared to be mainly two compounds, no clear assignment of which resonances belonged to which stereoisomer could be made with certainty. It was decided that catalytic hydrogenation to the diastereoisomeric derivatives of isoleucine would be the most satisfactory method for the determination of the diastereoisomeric ratio and of the C-2, C-3 stereochemistry of each diastereoisomer. This, in turn, required the synthesis of the authentic isoleucine derivatives.

The commercially available individual isomeric isoleucines were converted to their *N*-Boc, 8-phenylmenthyl ester derivatives. HPLC analysis revealed that the (2*S*, 3*R*)and (2*S*, 3*S*) compounds **9a** and **9b,** which were not separable, were the most chromatographically mobile diastereoisomers. Next to elute was the (2*R*, 3*S*) diastereoisomer **9d** and the last to elute was the (2*R*, 3*R*) diastereoisomer **9c**. ^{1}H NMR analysis of the diastereoisomers showed that the α proton of each diastereoisomer resonated as a doublet of doublets at distinctly different chemical shifts, which would ultimately allow an estimate of the (2*S*, 3*S*) to (2*S*, 3*R*) ratio of the butenyl transfer product **8**.

Catalytic hydrogenation of **8** gave the corresponding isoleucine derivatives. HPLC analysis of the reduction product showed that the major product(s) of this reaction did indeed possess the (2*S*) configuration.

Also revealed was a small peak attributed to unreduced material and another corresponding to the (2*R*, 3*R*) diastereoisomer **9c**. It was not possible to determine the amount of the (2*R*, 3*S*) diastereoisomer **9d** as the region at the retention time at which it was expected was obscured by the tail of the main peak and the trace of unreduced material. The total (2*S*) to (2*R*) ratio was estimated as 93:7.

Analysis of the α proton region of the ^{1}H NMR spectrum of the hydrogenation product and correlation with the spectra of the authentic (2*S*)-isoleucine diastereoisomers confirmed that the two doublets of doublets corresponded with those of the (2*S*, 3*R*) and (2*S*, 3*S*) isoleucine derivatives **9a** and **9b**. Integration of this region yielded a (2*S*,3*R*) to (2*S*,3*S*) ratio of *ca.* 3:2, indicating a slight stereoselectivity for the butenyl transfer.

The stereochemical control in free-radical reactions has been discussed recently and, in connection with the radical **2,** it has been suggested that either hydrogen-bonding[16] or dipolar effects[17] in the capto-dative radical might explain the strong preference for the (*Z*) rotamer. It should be noted that these two effects are complementary and could be acting in concert. ESR studies[18] show that related capto-dative radicals adopt the *Z* configuration. However, another factor reinforcing the formation of this conformation is also possible. Molecular model calculations on the (2*S*)-bromoglycine derivative **1** predict that the lowest energy conformation for this compound is with the carbon to bromine bond pointing directly away from the face of the phenyl ring. This means that even in the ground state this molecule is ideally arranged to go directly to the radical conformation with a minimum of bond reorganisation. Of course, this begs the question of how the bromide **1** is formed in the first place.

Although we have not been able to verify it, there is some circumstantial evidence that the bromide **1** arises through a first-order asymmetric transformation. That is the first formed diastereoisomeric bromides equilibrate, presumably through the iminium ion, to essentially one pure diastereoisomer. There is a report[19] that bromination at room temperature gives bromide **1** as a mixture of diastereoisomers and, certainly, we have observed peaks in the NMR spectrum consistent with a *ca.* 1:3 mixture of diastereoisomers when this was repeated. However, these bromides are rather unstable and we have not succeeded in establishing that equilibration, to just one diastereoisomer, takes place on heating this mixture.

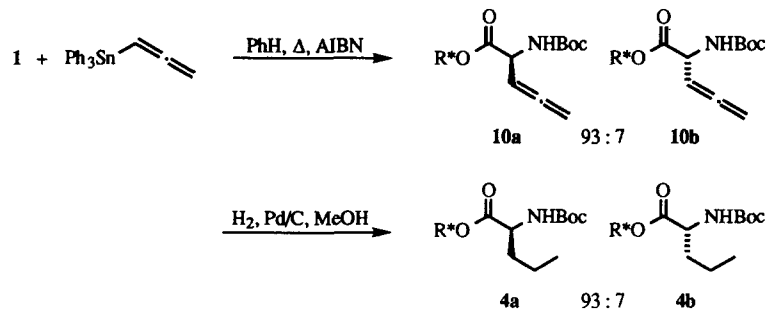
The observation that NBS bromination of 90% d.e. 8-phenylmenthyl (*S*)-*N*-Boc-2-deuterioglycine removed about three times as much deuterium as hydrogen[1] could be explained by a process in which kinetically the bromination is less selective but in which the product then equilibrates to essentially one isomer. No further loss of deuterium would occur during the equilibration and it would all end up in the pro-(*R*) position.

It is not clear which, if any, of the above three effects is the most important in controlling the stereochemistry of these reactions.

Allenyl and Propargyl Transfer Reactions

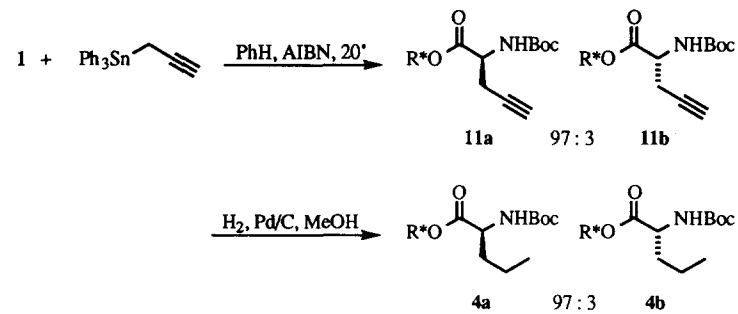
Based on the development of an allenyl transfer reaction[3], the synthesis of the 2-allenylglycine derivative **10** *via* the reaction of the bromide **1** with triphenyl(2-propynyl)stannane was attempted. When refluxed in benzene along with triphenyl(2-propynyl)stannane[20] and a catalytic amount of AIBN, the 2-bromoglycinate **1** gave a mixture of products in a 2:1 ratio (determined by ^{1}H NMR analysis) in a combined yield of 45% after chromatography. However, the two products clearly were not C-2 epimers of the anticipated 2-allenylglycine derivative **10**. It has been reported by Baldwin[21] that, in the presence of AIBN, thermolysis of triphenyl(2-propynyl)stannane results in partial isomerization to triphenyl-

(1,2-propadienyl)stannane *via* the competing S_H2' reaction of triphenylstannyl radical with the acetylene. Although it was stated that triphenyl(1,2-propadienyl)stannane was unreactive to carbon centred radicals, we surmised that one of the products in our mixture could have arisen from the reaction of this stannane with the bromide **1** through an alternative, non-radical mechanism. It was thus necessary to determine what, if any, product resulted from treatment of the bromide with triphenyl(1,2-propadienyl)stannane[20] under the same conditions (**Scheme 4**).



Scheme 4

Analysis of the product of this reaction by ^1H NMR revealed predominantly one compound, the spectrum of which matched that of the minor compound produced in the previous reaction. IR, ^1H NMR, ^{13}C NMR and MS evidence overwhelmingly showed that the 2-allenylglycine derivative **10** was the product of this reaction. Analysis of the product by HPLC revealed that it contained two components in a 93:7 ratio. Hydrogenation of this mixture yielded a 93:7 mixture of two compounds which correlated (by HPLC and ^1H NMR analysis) with the (*S*) and (*R*) norvaline derivatives **4a** and **4b** respectively, establishing that the predominant allenic diastereoisomer has the (2*S*) stereochemistry.



Scheme 5

Having established that the minor product formed upon treatment of the bromide **1** with triphenyl(2-propynyl)stannane in refluxing benzene was the 2-allenyl compound **10**, it remained to establish the identity of the major product formed in this reaction. Since it was suspected that it was the propargylglycine derivative **11**, formed by the reaction of the bromide with triphenyl(2-propynyl)stannane, it was proposed that if this reaction was run at a lower temperature to suppress the isomerisation of the stannane, **11** would be formed selectively. When run at 20°C, this was indeed the case (**Scheme 5**). ^1H and

^{13}C NMR, IR, MS and microanalysis confirmed the structure to be that of the propargylglycine derivative **11**. In addition, the ^{1}H NMR spectrum of the product of this reaction was identical to that of the major compound formed in the reaction of bromide **1** with triphenyl(2-propynyl)stannane at 80°C.

Analysis of the product by HPLC revealed the presence of two components in a 97:3 ratio. Hydrogenation of the mixture gave a product which contained two components, also in a 97:3 ratio, with the major component correlating by HPLC and ^{1}H and ^{13}C NMR with the (*S*) norvaline derivative **4a**. The minor component correlated by HPLC with the (*R*) norvaline derivative **4b**.

Clearly the bromide **1** reacts with triphenyl(2-propynyl)stannane to give the corresponding (2*S*)-propargylglycine derivative **11** and with triphenyl(1,2-propadienyl)stannane to give the isomeric (2*S*)-allenylglycinate **10**. 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 atom. A reaction mechanism which does not involve radicals, but rather, invokes ionic intermediates, is proposed in **Scheme 6**. The fact that phenyl transfer does not occur does not rule out this mechanism. Both the allenyl and propargyl anions are stabilised by delocalisation 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 phenyl anion, no such overlap is possible since the π system is orthogonal to the σ orbital housing the negative charge. It seems unlikely, however, that this mechanism is operating in the allyl transfer reactions discussed previously, since the product of coupling α to the tin atom in the reaction of the bromide **1** with (*E*)-(2-butenyl)tri-*n*-butylstannane was not detected.

Scheme 6

In an attempt to establish whether or not the above reactions involved radical intermediates, the bromide **1** was treated with allyltri-*n*-butylstannane in the absence of AIBN, but in the presence of 10 mole % of the radical inhibitor hydroquinone in the dark. Under these conditions, the allyl transfer to give mainly the (2*S*) allylglycinate **3** proceeded at the same rate to give the same ratio of diastereoisomers as when the reaction was conducted in the presence of AIBN and with no measures taken to preclude light. However, the result of this experiment is inconclusive. Radical reactions may still proceed in the presence of radical inhibitors if the radicalophile employed is a more efficient radical scavenger than the radical inhibitor. However, irrespective of the finer details of the mechanisms involved, this process yields α-amino acid derivatives of high optical purity.

Acknowledgements

P.R. was supported financially by an Australian Postgraduate Research Award. This project was also supported financially, in part, by an Australian Research Council grant to D.P.G.H and R.A.M-W. We thank Mrs J. L. Newton for the attempted equilibration studies and Dr C. Hutton, presently at the Department of Chemistry, U.C. Berkeley, for Macromodel™ calculations.

EXPERIMENTAL

General

General experimental conditions are described in a previous paper[1]. For all HPLC analyses the mobile phase was a 19:1 mixture of hexane and ethyl acetate respectively.

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-[(Tert-butoxycarbonyl)amino]pent-4-enoate 3. The reactions given in the table were all conducted in essentially the same manner, except for the differences noted. The procedure for the optimum conditions (Entry 3) is given. A solution of bromide **1**[1] (77 mg, 0.164 mmol), allyltri-*n*-butylstannane (120 mg, 0.361 mmol) and AIBN (*ca.* 1 mg) in dry benzene (6.2 ml) was left to stand at 20°C for 16h. The benzene was evaporated and the residue chromatographed on silica to give **3** (60 mg, 85%). The ^{1}H NMR spectrum was identical to the spectrum of the authentic (2*S*) ester **3a**. HPLC analysis indicated that the (2*S*) to (2*R*) ratio (**3a** to **3b**) was 96:4. Compounds **3a** and **3b** were fully characterised elsewhere[12].

Catalytic Hydrogenation of Allylglycine Derivative 3. The procedure used generally is illustrated by one example. Allylglycine derivative **3** (a 93:7 (2*S*) to (2*R*) mixture of diastereoisomers, 15 mg, 36 μmol) was reduced over 10% Pd/C (7 mg) in methanol (1 ml) with H_2 at atmospheric pressure for 16h, to give **4** (13 mg, 88%) as a colourless oil. HPLC analysis indicated the presence of two components in a 93:7 ratio. The major component co-eluted with an authentic sample of (2*S*) norvaline derivative **4a**[12] and the minor component co-eluted with an authentic sample of the corresponding (2*R*) diastereoisomer **4b**[12].

(S)-Allylglycine 5. Allylglycine derivative **3a** (>99% (2*S*) by HPLC) (283 mg, 0.659 mmol) was dissolved in trifluoroacetic acid (2 ml) and the mixture left to stand at room temp. for 10 min.; 6mol.dm^{-3} HCl (4 ml) was then added and the mixture refluxed for 15 h. After cooling to room temperature, water was added and the resultant solution washed twice with chloroform. The aqueous layer was evaporated to dryness *in vacuo*. The residue was purified by ion exchange chromatography on Amberlite 1R-120 (H) to give **5** (49.6 mg, 65%). MS 134 (by-product $[M + H]^+$, 18), 116 (allylglycine $[M + H]^+$, 100). ^{1}H NMR (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 allylglycine, except for the presence of an extraneous signal (δ 1.11, d, *J* 6.0 Hz, 0.17H). No other distinct resonances complementary to this signal were discernible in the spectrum. $[\alpha]_D^{24} = -30.3°$ (C=3.77, H_2O). Lit.[13]: $[\alpha]_D^{24} = -37.1°$ (C=4, H_2O). The product (41 mg, 0.359 mmol) was converted to its *N*-Boc derivative[22] (59 mg, 77%). Then this derivative (48 mg 0.223 mmol) was esterified with (−)-8-phenylmenthol (57 mg, 0.246 mmol) under standard DCC/DMAP conditions[23] to give **3** (85 mg, 89%). HPLC analysis showed that the (2*S*) to (2*R*) ratio was 98.3:1.7).

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-[(Tert-butoxycarbonyl)amino]-4-methyl-pent-4-enoate 6. A solution of the bromoglycine derivative **1** (91 mg, 0.193 mmol), tri-*n*-butyl(2-methyl-2-propenyl)stannane (133 mg, 0.386 mmol) and AIBN (*ca.* 1 mg) in dry benzene (0.68 ml) was let stand at 20°C for 16h. The benzene was evaporated and the residue chromatographed on silica to give **6** (69 mg, 81%). HPLC analysis indicated the presence of two components in a 95:5 ratio. MS 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 NMR 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 (**H**C-O); 7.15-7.35, complex, 5H (Ar**H**). ^{13}C NMR 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 **C**HCPh); 51.68 (α CH); 75.72 (H-**C**-O); 79.21 (**C**Me$_3$); 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)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (R,S)-2-[(Tert-butoxycarbonyl)amino]-4-methylpentanoate 7. (*R,S*)-*N*-Boc-leucine was esterified with (−)-8-phenylmenthol. Flash chromatography[24] gave **7** as a colourless oil (87%): 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*) diastereoisomers were obtained by preparative HPLC: (2*S*) diastereoisomer **7a**: MS/FAB : m/z 446 ([M + H]$^+$), 390 ([M + H]$^+ - C_4H_8$). ^{1}H NMR 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 (**H**C-O); 7.10-7.35, complex, 5H (Ar**H**). (2*R*) diastereoisomer **7b**: MS/FAB : m/z 446 ([M + H]$^+$), 390 ([M + H]$^+$ - C_4H_8). ^{1}H NMR 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 (**H**C-O); 7.15-7.30, complex, 5H (Ar**H**).

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (S)-2-[(Tert-butoxycarbonyl)amino]-4-methyl-pentanoate 7a. (*S*)-*N*-Boc-leucine was esterified with (−)-8-phenylmenthol. Flash chromatography gave the *title compound* as a colourless oil in 73% yield. NMR data were identical to those above for the (2*S*) diastereoisomer isolated from the mixture of diastereoisomers.

Catalytic Hydrogenation of γ,δ-Dehydroleucine Derivative 6. Amino acid derivative **6** (a 95:5 (2*S*) to (2*R*) mixture of diastereoisomers, 20 mg, 46 μmol) was reduced over 10% Pd/C (10 mg) in methanol (1 ml) by the method above to give compound **7** (20 mg, 100%) as a colourless oil. HPLC showed the presence of two components in a 94:6 ratio. The major component co-eluted with an authentic sample of (2*S*) leucine derivative **7a**, and the minor component co-eluted with an authentic sample of the corresponding (2*R*) diastereoisomer **7b**. The ^{1}H NMR spectrum of the mixture appeared identical to the spectrum of authentic **7a**.

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-[(Tert-butoxycarbonyl)amino]-3-methyl-pent-4-enoate 8. A solution of the bromoglycine derivative **1** (60 mg, 0.127 mmol), (*E*)-(2-butenyl)tri-*n*-butylstannane (97 mg, 0.280 mmol) and AIBN (*ca.* 1 mg) in dry benzene (1.00 ml) was let stand at 20°C for 16 h. The benzene was evaporated *in vacuo* and the residue chromatographed on silica to give **8** (47 mg, 83%). MS 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 NMR 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 NMR 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).

Catalytic Hydrogenation of γ,δ-Dehydroisoleucine Derivative 8. The ester **8** (35 mg, 90 μmol) was reduced over platinum oxide (10 mg, 45μmol) in methanol (2 ml) as described above to give the saturated derivative **9** (33 mg, 83%) as a colourless oil. HPLC analysis indicated the presence of three components in a *ca.* 83:11:6 ratio. The first-eluting (major) component co-eluted with authentic samples of (2*S*, 3*R*) isoleucine derivative **9a** and the corresponding (2*S*, 3*S*) diastereoisomer **9b**. The second-eluting component co-eluted with starting material. The third-eluting component co-eluted with an authentic sample of (2*R*, 3*R*) isoleucine derivative **9c**. Thus the (2*S*) to (2*R*) ratio was 93:7. The ^1H NMR spectrum of **9**, when compared with the spectra of authentic **9a** and **9b**, indicated that the (2*S*, 3*R*) to (2*S*, 3*S*) ratio was *ca.* 3:2.

8-Phenylmenthyl* N-*Boc Isoleucinates 9a-9d. The appropriate *N*-Boc-isoleucines were esterified with (−)-8-phenylmenthol. Flash chromatography gave **9a-9d** as colourless oils. ***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2S, 3R)-2-[(Tert-butoxycarbonyl)amino]-3-methylpentanoate 9a*** (61%). 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. ^1H NMR 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)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2S, 3S)-2-[(Tert-butoxycarbonyl)amino]-3-methylpentanoate 9b*** (48%). 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. ^1H NMR 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)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2R, 3R)-2-[(Tert-butoxycarbonyl)-amino]-3-methylpentanoate 9c*** (54%). 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. ^1H NMR 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)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (2R, 3S)-2-[(Tert-butoxycarbonyl)amino]-3-methylpentanoate 9d*** (66%). 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. ^1H NMR 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)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-[(Tert-butoxycarbonyl)amino]penta-3,4-dienoate 10. A solution of the bromoglycine derivative **1** (79 mg, 0.168 mmol), triphenyl(1,2-propadienyl)-stannane (131 mg, 0.336 mmol) and AIBN (*ca.* 1 mg) in dry benzene (0.59 ml) was refluxed for 5 h. The benzene was evaporated and the residue chromatographed on silica to give **10** (38 mg, 53%). HPLC showed two components in a 93:7 ratio. MS m/z 427 (M^+), 426 ($M^+ - H$), 371 ($M^+ - C_4H_8$). Exact mass calculated for $C_{26}H_{38}NO_4$ ($[M + H]^+$) 428.280, found 428.283. ^1H NMR 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 NMR 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). IR ν 1958 cm^{-1}.

Catalytic Hydrogenation of the Allenylglycine Derivative 10. The allenylglycine derivative **10** (11 mg, 27 μmol) was reduced over 10% Pd/C (5 mg) in methanol (1 ml) by the method above to give the corresponding norvaline derivative **4** (9 mg, 78%) as a colourless oil. HPLC showed two components in a 93:7 ratio. The major component co-eluted with an authentic sample of the (2*S*) norvaline derivative **4a** and the minor component co-eluted with an authentic sample of the corresponding (2*R*) diastereoisomer **4b**. The ^1H NMR spectrum of the mixture appeared identical to that of authentic **4a**.

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-[(Tert-butoxycarbonyl)amino]pent-4-ynoate 11. A solution of the bromoglycine derivative **1** (60 mg, 0.128 mmol), triphenyl(2-propynyl)stannane (100 mg, 0.256 mmol) and AIBN (*ca.* 1 mg) in dry benzene (0.45 ml) was let stand at 20°C for 16h. The benzene was evaporated and the residue chromatographed on silica to give **11** (32 mg, 58%) as a colourless oil which solidified on standing. HPLC showed two components in a 97:3 ratio. Recrystallization from hexane gave white crystals, m.p. 126-127°C. MS m/z 427 (M^+), 371 ($M^+ - C_4H_8$). $C_{22}H_{29}NO_4$ ($M^+ - C_4H_8$) requires 371.210, found 371.212. $C_{26}H_{37}NO_4$ requires C 73.04%, H 8.72%; found C 73.26%, H 8.80%. ^1H NMR 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 NMR 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). IR ν 3300 cm^{-1}.

Catalytic Hydrogenation of the Propynylglycine Derivative 11. The 97:3 (2*S*) to (2*R*) mixture of diastereoisomers of the alkyne **11** (22 mg, 52 μmol) was reduced over 10% Pd/C (10 mg) in methanol (1 ml) by the above method to give **4** (16 mg, 71%) as a colourless oil. HPLC showed two components in a 97:3 ratio. The major component co-eluted with an authentic sample of (2*S*) norvaline derivative **4a**[12] and the minor component co-eluted with an authentic sample of the corresponding (2*R*) diastereoisomer **4b**. The ^1H

NMR spectrum of the mixture appeared identical to that of authentic **4a**.

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(*Received in UK* 24 *January* 1995; *accepted* 9 *February* 1995)